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## 5 A2

### (54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly lung cancer, are disclosed. Illustrative compositions comprise one or more lung tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly lung cancer.

# COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

### TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of lung cancer.

### 10 BACKGROUND OF THE INVENTION

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Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

### SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

- (a) sequences provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583;
- (b) complements of the sequences provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583;
- 5 (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583;
  - (d) sequences that hybridize to a sequence provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583, under moderately stringent conditions;

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- (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583;
- (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583; and
- 15 (g) degenerate variants of a sequence provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583.

In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of lung tumors samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for normal tissues.

The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

In specific embodiments, the present invention provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 391, 393, 395, 397, 421, 425-427, 434-439 and 584-587.

In certain preferred embodiments, the polypeptides and/or 30 polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of

eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NOs: 391, 393, 395, 397, 421, 425-427, 434-439 and 584-587 or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

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Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, the pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic applications. Such compositions generally comprise an immunogenic polypeptide or polynucleotide of the invention and an immunostimulant, such as an adjuvant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

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Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, e.g., vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating the expression, purification and/or immunogenicity of the polypeptide(s).

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Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition as recited above. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

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Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

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The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a lung cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time

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with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

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In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

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Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

### SEQUENCE IDENTIFIERS

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10 SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons SEQ ID NO: 3 is the determined cDNA sequence for L263C2c SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons SEQ ID NO: 5 is the determined cDNA sequence for L263C1b 15 SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons SEQ ID NO: 8 is the determined cDNA sequence for L366C1a SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons SEQ ID NO: 10 is the determined cDNA sequence for L163C1c 20 SEQ ID NO: 11 is the determined cDNA sequence for L163C1b SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons SEQ ID NO: 13 is the determined cDNA sequence for L255C1b SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons 25 SEQ ID NO: 16 is the determined cDNA sequence for L163C1a SEQ ID NO: 17 is the determined cDNA sequence for LT86-1 SEO ID NO: 18 is the determined cDNA sequence for LT86-2 SEQ ID NO: 19 is the determined cDNA sequence for LT86-3 SEQ ID NO: 20 is the determined cDNA sequence for LT86-4

	SEQ ID NO: 21 is the determined cDNA sequence for LT86-5
	SEQ ID NO: 22 is the determined cDNA sequence for LT86-6
·	SEQ ID NO: 23 is the determined cDNA sequence for LT86-7
	SEQ ID NO: 24 is the determined cDNA sequence for LT86-8
5	SEQ ID NO: 25 is the determined cDNA sequence for LT86-9
	SEQ ID NO: 26 is the determined cDNA sequence for LT86-10
	SEQ ID NO: 27 is the determined cDNA sequence for LT86-11
	SEQ ID NO: 28 is the determined cDNA sequence for LT86-12
	SEQ ID NO: 29 is the determined cDNA sequence for LT86-13
10	SEQ ID NO: 30 is the determined cDNA sequence for LT86-14
	SEQ ID NO: 31 is the determined cDNA sequence for LT86-15
	SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1
	SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2
	SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3
15	SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4
	SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5
	SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6
	SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7
	SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8
20	SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9
	SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10
	SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11
	SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12
	SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13
25	SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14
	SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15
	SEQ ID NO: 47 is a (dT) <sub>12</sub> AG primer
	SEQ ID NO: 48 is a primer
	SEQ ID NO: 49 is the determined 5' cDNA sequence for L86S-3
30	SEQ ID NO: 50 is the determined 5' cDNA sequence for L86S-12

		SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16
		SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25
		SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36
		SEQ ID NO: 54 is the determined 5' cDNA sequence for L86S-40
5		SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46
		SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3
		SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12
		SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16
		SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25
10		SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36
		SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40
		SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46
		SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30
		SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41
15		SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of
	LT86-9	
		SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4
		SEQ ID NO: 67 is the predicted extended amino acid sequence for
	LT86-4	
20		SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20
		SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21
		SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22
		SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26
		SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27
25		SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20
		SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21
		SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22
		SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26
		SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27
30		SEQ ID NO: 78 is the determined extended cDNA sequence for L86S-12

SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36 SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46 SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12

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SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-

36

SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46

10

SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6

SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11

SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14

SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29

SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34

SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39

15

SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47

SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49

SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51

SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6 SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11

20

SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14

SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29

SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34

SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39

SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47

25

SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49

SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51

SEQ ID NO: 102 is the determined DNA sequence for SLT-T1

SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3

30

SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5

	SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7
	SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9
	SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10
	SEQ ID NO: 109 is the determined 5' cDNA sequence for SLT-T11
5	SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12
	SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1
	SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2
	SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3
	SEQ ID NO: 114 is the predicted amino acid sequence for SLT-T10
10	SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12
	SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T
	SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-Te
	SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T
	SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T
15	SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-TS
·.	SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T
	SEQ ID NO: 122 is the predicted amino acid sequence for SALT-Ta
	SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T
	SEQ ID NO: 124 is the predicted amino acid sequence for SALT-To
20	SEQ ID NO: 125 is the predicted amino acid sequence for SALT-TS
	SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1
	SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2
	SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7
	SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13
25	SEQ ID NO: 130 is the determined cDNA sequence for PSLT-27
	SEQ ID NO: 131 is the determined cDNA sequence for PSLT-28
	SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30
	SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40
	SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69
30	SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71

	SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73
	SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79
	SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03
	SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09
5	SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011
	SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041
•	SEQ ID NO: 142 is the determined cDNA sequence for PSLT-62
	SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6
	SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37
10	SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74
	SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010
	SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012
	SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037
	SEQ ID NO: 149 is the determined 5' cDNA sequence for SAL-3
15	SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24
	SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25
	SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33
	SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50
	SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57
20	SEQ ID NO: 155 is the determined 5' cDNA sequence for SAL-66
	SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82
	SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99
	SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104
	SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109
25	SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5
	SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8
	SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12
	SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14
	SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16
30	SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23

	SEQ ID NO: 166 is the determined 5° cDNA sequence for SAL-26
	SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29
	SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32
	SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39
5	SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42
	SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43
	SEQ ID NO: 172 is the determined 5' cDNA sequence for SAL-44
	SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48
,	SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68
.0	SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72
	SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77
	SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86
	SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88
	SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93
15	SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100
	SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105
·	SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3
	SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24
	SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25
20	SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25 $$
	SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33
	SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50
	SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57
	SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66
25	SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66
	SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82
	SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99
	SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104
	SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5
30	SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8

	SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12
	SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14
	SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16
	SEQ ID NO: 199 is the predicted amino acid sequence for SAL-23
5	SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26
•	SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29
	SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32
	SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39
	SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42
10	SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43
	SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44
	SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48
	SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68
	SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72
15	SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77
	SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86
	SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88
	SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93
	SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100
20	SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105
	SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50
	SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4
	SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9
	SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10
25	SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12
	SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19
	SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31
	SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38
	SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2
30	SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3

	SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22
	SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24
	SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37
	SEQ ID NO: 229 is the determined cDNA sequence for LT4690-39
5	SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40
	SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41
	SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49
	SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55
	SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55
10	SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59
	SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63
	SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71
	SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3
•	SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6
15	SEQ ID NO: 240 is the determined cDNA sequence for 2LT-22
	SEQ ID NO: 241 is the determined cDNA sequence for 2LT-25
	SEQ ID NO: 242 is the determined cDNA sequence for 2LT-26
	SEQ ID NO: 243 is the determined cDNA sequence for 2LT-31
	SEQ ID NO: 244 is the determined cDNA sequence for 2LT-36
20	SEQ ID NO: 245 is the determined cDNA sequence for 2LT-42
	SEQ ID NO: 246 is the determined cDNA sequence for 2LT-44
	SEQ ID NO: 247 is the determined cDNA sequence for 2LT-54
	SEQ ID NO: 248 is the determined cDNA sequence for 2LT-55
	SEQ ID NO: 249 is the determined cDNA sequence for 2LT-57
25	SEQ ID NO: 250 is the determined cDNA sequence for 2LT-58
	SEQ ID NO: 251 is the determined cDNA sequence for 2LT-59
	SEQ ID NO: 252 is the determined cDNA sequence for 2LT-62
	SEQ ID NO: 253 is the determined cDNA sequence for 2LT-63
	SEQ ID NO: 254 is the determined cDNA sequence for 2LT-65
30	SEQ ID NO: 255 is the determined cDNA sequence for 2LT-66

SEQ ID NO: 256 is the determined cDNA sequence for 2LT-70 SEQ ID NO: 257 is the determined cDNA sequence for 2LT-73 SEQ ID NO: 258 is the determined cDNA sequence for 2LT-74 SEQ ID NO: 259 is the determined cDNA sequence for 2LT-76 5 SEQ ID NO: 260 is the determined cDNA sequence for 2LT-77 SEQ ID NO: 261 is the determined cDNA sequence for 2LT-78 SEQ ID NO: 262 is the determined cDNA sequence for 2LT-80 SEQ ID NO: 263 is the determined cDNA sequence for 2LT-85 SEQ ID NO: 264 is the determined cDNA sequence for 2LT-87 10 SEQ ID NO: 265 is the determined cDNA sequence for 2LT-89 SEQ ID NO: 266 is the determined cDNA sequence for 2LT-94 SEQ ID NO: 267 is the determined cDNA sequence for 2LT-95 SEQ ID NO: 268 is the determined cDNA sequence for 2LT-98 SEQ ID NO: 269 is the determined cDNA sequence for 2LT-100 15 SEQ ID NO: 270 is the determined cDNA sequence for 2LT-103 SEQ ID NO: 271 is the determined cDNA sequence for 2LT-105 SEQ ID NO: 272 is the determined cDNA sequence for 2LT-107 SEQ ID NO: 273 is the determined cDNA sequence for 2LT-108 SEQ ID NO: 274 is the determined cDNA sequence for 2LT-109 20 SEQ ID NO: 275 is the determined cDNA sequence for 2LT-118 SEQ ID NO: 276 is the determined cDNA sequence for 2LT-120 SEQ ID NO: 277 is the determined cDNA sequence for 2LT-121 SEQ ID NO: 278 is the determined cDNA sequence for 2LT-122 SEQ ID NO: 279 is the determined cDNA sequence for 2LT-124 25 SEQ ID NO: 280 is the determined cDNA sequence for 2LT-126 SEQ ID NO: 281 is the determined cDNA sequence for 2LT-127 SEQ ID NO: 282 is the determined cDNA sequence for 2LT-128 SEQ ID NO: 283 is the determined cDNA sequence for 2LT-129 SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133 30 SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137

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SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71 SEQ ID NO: 287 is the determined cDNA sequence for LT4690-82 SEQ ID NO: 288 is the determined full-length cDNA sequence for SSLT-74 5 SEQ ID NO: 289 is the determined cDNA sequence for SSLT-78 SEQ ID NO: 290 is the determined cDNA sequence for SCC1-8. SEQ ID NO: 291 is the determined cDNA sequence for SCC1-12. SEQ ID NO: 292 is the determined cDNA sequence for SCC1-336 SEQ ID NO: 293 is the determined cDNA sequence for SCC1-344 10 SEQ ID NO: 294 is the determined cDNA sequence for SCC1-345 SEQ ID NO: 295 is the determined cDNA sequence for SCC1-346 SEQ ID NO: 296 is the determined cDNA sequence for SCC1-348 SEQ ID NO: 297 is the determined cDNA sequence for SCC1-350 SEQ ID NO: 298 is the determined cDNA sequence for SCC1-352 15 SEQ ID NO: 299 is the determined cDNA sequence for SCC1-354 SEQ ID NO: 300 is the determined cDNA sequence for SCC1-355 SEQ ID NO: 301 is the determined cDNA sequence for SCC1-356 SEQ ID NO: 302 is the determined cDNA sequence for SCC1-357 SEQ ID NO: 303 is the determined cDNA sequence for SCC1-501 20 SEQ ID NO: 304 is the determined cDNA sequence for SCC1-503 SEQ ID NO: 305 is the determined cDNA sequence for SCC1-513 SEQ ID NO: 306 is the determined cDNA sequence for SCC1-516 SEQ ID NO: 307 is the determined cDNA sequence for SCC1-518 SEQ ID NO: 308 is the determined cDNA sequence for SCC1-519 SEQ ID NO: 309 is the determined cDNA sequence for SCC1-522 25 SEQ ID NO: 310 is the determined cDNA sequence for SCC1-523 SEQ ID NO: 311 is the determined cDNA sequence for SCC1-525 SEQ ID NO: 312 is the determined cDNA sequence for SCC1-527 SEQ ID NO: 313 is the determined cDNA sequence for SCC1-529 30 SEQ ID NO: 314 is the determined cDNA sequence for SCC1-530

	SEQ ID NO: 315 is the determined cDNA sequence for SCC1-531
	SEQ ID NO: 316 is the determined cDNA sequence for SCC1-532
	SEQ ID NO: 317 is the determined cDNA sequence for SCC1-533
-	SEQ ID NO: 318 is the determined cDNA sequence for SCC1-536
5	SEQ ID NO: 319 is the determined cDNA sequence for SCC1-538
	SEQ ID NO: 320 is the determined cDNA sequence for SCC1-539
	SEQ ID NO: 321 is the determined cDNA sequence for SCC1-541
	SEQ ID NO: 322 is the determined cDNA sequence for SCC1-542
	SEQ ID NO: 323 is the determined cDNA sequence for SCC1-546
10	SEQ ID NO: 324 is the determined cDNA sequence for SCC1-549
	SEQ ID NO: 325 is the determined cDNA sequence for SCC1-551
	SEQ ID NO: 326 is the determined cDNA sequence for SCC1-552
	SEQ ID NO: 327 is the determined cDNA sequence for SCC1-554
	SEQ ID NO: 328 is the determined cDNA sequence for SCC1-558
15	SEQ ID NO: 329 is the determined cDNA sequence for SCC1-559
	SEQ ID NO: 330 is the determined cDNA sequence for SCC1-561
	SEQ ID NO: 331 is the determined cDNA sequence for SCC1-562
	SEQ ID NO: 332 is the determined cDNA sequence for SCC1-564
	SEQ ID NO: 333 is the determined cDNA sequence for SCC1-565
20	SEQ ID NO: 334 is the determined cDNA sequence for SCC1-566
	SEQ ID NO: 335 is the determined cDNA sequence for SCC1-567
	SEQ ID NO: 336 is the determined cDNA sequence for SCC1-568
	SEQ ID NO: 337 is the determined cDNA sequence for SCC1-570
	SEQ ID NO: 338 is the determined cDNA sequence for SCC1-572
25	SEQ ID NO: 339 is the determined cDNA sequence for SCC1-575
	SEQ ID NO: 340 is the determined cDNA sequence for SCC1-576
	SEQ ID NO: 341 is the determined cDNA sequence for SCC1-577
	SEQ ID NO: 342 is the determined cDNA sequence for SCC1-578
	SEQ ID NO: 343 is the determined cDNA sequence for SCC1-582
30	SEQ ID NO: 344 is the determined cDNA sequence for SCC1-583

		SEQ ID NO: 345 is the determined cDNA sequence for SCC1-586
		SEQ ID NO: 346 is the determined cDNA sequence for SCC1-588
		SEQ ID NO: 347 is the determined cDNA sequence for SCC1-590
		SEQ ID NO: 348 is the determined cDNA sequence for SCC1-591
5		SEQ ID NO: 349 is the determined cDNA sequence for SCC1-592
		SEQ ID NO: 350 is the determined cDNA sequence for SCC1-593
		SEQ ID NO: 351 is the determined cDNA sequence for SCC1-594
		SEQ ID NO: 352 is the determined cDNA sequence for SCC1-595
		SEQ ID NO: 353 is the determined cDNA sequence for SCC1-596
10		SEQ ID NO: 354 is the determined cDNA sequence for SCC1-598
		SEQ ID NO: 355 is the determined cDNA sequence for SCC1-599
		SEQ ID NO: 356 is the determined cDNA sequence for SCC1-602
		SEQ ID NO: 357 is the determined cDNA sequence for SCC1-604
		SEQ ID NO: 358 is the determined cDNA sequence for SCC1-605
15		SEQ ID NO: 359 is the determined cDNA sequence for SCC1-606
		SEQ ID NO: 360 is the determined cDNA sequence for SCC1-607
		SEQ ID NO: 361 is the determined cDNA sequence for SCC1-608
		SEQ ID NO: 362 is the determined cDNA sequence for SCC1-610
		SEQ ID NO: 363 is the determined cDNA sequence for clone DMS79T1
20		SEQ ID NO: 364 is the determined cDNA sequence for clone DMS79T2
		SEQ ID NO: 365 is the determined cDNA sequence for clone DMS79T3
		SEQ ID NO: 366 is the determined cDNA sequence for clone DMS79T5
		SEQ ID NO: 367 is the determined cDNA sequence for clone DMS79T6
		SEQ ID NO: 368 is the determined cDNA sequence for clone DMS79T7
25		SEQ ID NO: 369 is the determined cDNA sequence for clone DMS79T9
		SEQ ID NO: 370 is the determined cDNA sequence for clone
	DMS79T10	
		SEQ ID NO: 371 is the determined cDNA sequence for clone
	DMS79T11	
30		SEQ ID NO: 372 is the determined cDNA sequence for clone 128T1

		SEQ I	ID N	Ю: 37	3 is th	ne d	etern	nined cDNA	sequence	e for clone	1287	2
		SEQ I	ID N	O: 37	4 is th	ie d	etern	nined cDNA	sequence	e for clone	1287	73
		SEQ I	ID N	iO: 37	5 is th	ie d	etern	nined cDNA	sequence	e for clone	1287	4
		SEQ I	ID N	IO: 37	6 is tł	ie d	etern	nined cDNA	sequence	e for clone	1287	75
5		SEQ	ID N	IO: 37	7 is th	ne d	etern	nined cDNA	sequence	e for clone	1287	7
		SEQ	ID N	IO: 37	8 is th	ie d	etern	nined cDNA	sequence	e for clone	1287	9
		SEQ I	ID N	IO: 37	9 is th	ie d	etern	nined cDNA	sequence	e for clone	1287	710
		SEQ :	ID N	IO: 38	0 is th	ne d	etern	nined cDNA	sequence	e for clone	1287	711
		SEQ	ID N	IO: 38	1 is th	ie d	etern	nined cDNA	sequence	e for clone	1287	12
10		SEQ	ID	NO:	3.82	is	the	determined	cDNA	sequence	for	clone
	NCIH69T3											
		SEQ	ID	NO:	383	is	the	determined	cDNA	sequence	for	clone
	NCIH69T5											
		SEQ	ID	NO:	384	is	the	determined	cDNA	sequence	for	clone
15	NCIH69T6											
		SEQ	ID	NO:	385	įs	the	determined	cDNA	sequence	for	clone
	NCIH69T7											
		SEQ	ID	NO:	386	is	the	determined	cDNA	sequence	for	clone
	NCIH69T9											
20	2.10777.0074.0	SEQ	ID	NO:	387	is	the	determined	cDNA	sequence	tor	clone
	NCIH69T10		TTS	210	200		.1	1 4	TO N.T. A		c	1
	NOTE COT 1	SEQ	ID	NO:	388	18	tņe	determined	ÇDNA	sequence	ior	clone
	NCIH69T11	SEO.	II.	NIO.	200	• -	41	4-4	aTŠNI A		£	مامسم
a É	NOTITIOT12	SEQ	שנ	ŊO:	389	18	tne	determined	CDNA	sequence	101	cione
25	NCIH69T12	SEO.	II) N	IO. 20	∩ : a +1	<del>.</del> 6		ngth cDNA s	100110000	for 120T1		
		`				-		acid sequen	÷			
								•			28	
								ngth cDNA so acid sequen	•		<b>ل</b>	
30		_						ed cDNA sec			:C1-5	342.
JU		DUC.	.ı v	· • • • •	13 a	11 UA	アハココイ	いは ハンエハン りいじ	incrice IC	T OTOTIC DC		

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SEQ ID NO: 395 is the amino acid sequence corresponding to SEQ ID NO:394 SEQ ID NO: 396 is an extended cDNA sequence for clone SCC1-593 SEQ ID NO: 397 is the amino acid sequence corresponding to SEQ ID 5 NO:396 SEQ ID NO:398 is the determined cDNA sequence for 55508.1 SEQ ID NO:399 is the determined cDNA sequence for 55509.1 SEQ ID NO:400 is the determined cDNA sequence for 54243.1 SEQ ID NO:401 is the determined cDNA sequence for 54251.1 10 SEQ ID NO:402 is the determined cDNA sequence for 54252.1 SEQ ID NO:403 is the determined cDNA sequence for 54253.1 SEQ ID NO:404 is the determined cDNA sequence for 55518.1 SEQ ID NO:405 is the determined cDNA sequence for 54258.1 SEQ ID NO:406 is the determined cDNA sequence for 54575.1 15 SEQ ID NO:407 is the determined cDNA sequence for 54577.1 SEQ ID NO:408 is the determined cDNA sequence for 54584.1 SEQ ID NO:409 is the determined cDNA sequence for 55521.1 SEQ ID NO:410 is the determined cDNA sequence for 54589.1 SEQ ID NO:411 is the determined cDNA sequence for 54592.1 20 SEQ ID NO:412 is the determined cDNA sequence for 55134.1 SEQ ID NO:413 is the determined cDNA sequence for 55137.1 SEQ ID NO:414 is the determined cDNA sequence for 55140.1 SEQ ID NO:415 is the determined cDNA sequence for 55531.1 SEQ ID NO:416 is the determined cDNA sequence for 55532.1 25 SEQ ID NO:417 is the determined cDNA sequence for 54621.1 SEQ ID NO:418 is the determined cDNA sequence for 55548.1 SEQ ID NO:419 is the determined cDNA sequence for 54623.1 SEQ ID NO:420 is the determined cDNA sequence for L39 SEQ ID NO:421 is the predicted amino acid sequence for L39 30 SEQ ID NO:422 is the determined cDNA sequence for SCC2-29

	SEQ ID NO:423 is the determined cDNA sequence for SCC2-36
	SEQ ID NO:424 is the determined cDNA sequence for SCC2-60
	SEQ ID NO:425 is the predicted amino acid sequence for SCC2-29
	SEQ ID NO:426 is the predicted amino acid sequence for SCC2-36
5	SEQ ID NO:427 is the predicted amino acid sequence for SCC2-60
	SEQ ID NO:428 is an extended cDNA sequence for the clone 2012
	also referred to as 2LT-3, set forth in SEQ ID NO: 238
	SEQ ID NO:429 is an extended cDNA sequence for the clone 2034
	also referred to as 2LT-26, set forth in SEQ ID NO: 242
10	SEQ ID NO:430 is an extended cDNA sequence for the clone 2128
	also referred to as 2LT-57, set forth in SEQ ID NO: 249
	SEQ ID NO:431 is an extended cDNA sequence for the clone 2128
	also referred to as 2LT-58, set forth in SEQ ID NO: 250
	SEQ ID NO:432 is an extended cDNA sequence for the clone 2148
15	also referred to as 2LT-98, set forth in SEQ ID NO: 268
	SEQ ID NO:433 is an extended cDNA sequence for the clone 2187
	also referred to as 2LT-124, set forth in SEQ ID NO: 279
	SEQ ID NO:434 is an amino acid sequence encoded by SEQ ID NO: 42
	SEQ ID NO:435 is an amino acid sequence encoded by SEQ ID NO: 42
20	SEQ ID NO:436 is an amino acid sequence encoded by SEQ ID NO: 43
	SEQ ID NO:437 is an amino acid sequence encoded by SEQ ID NO: 43
	SEQ ID NO:438 is an amino acid sequence encoded by SEQ ID NO: 43
	SEQ ID NO:439 is an amino acid sequence encoded by SEQ ID NO: 43
	SEQ ID NO:440 is the determined cDNA sequence for clone 19A4
25	SEQ ID NO: 441 is the determined full-length cDNA sequence for clor
	14F10.
	SEQ ID NO: 442 is the determined 5' cDNA sequence for clone 20E10
	SEQ ID NO: 443 is a first determined cDNA sequence for clone 55153.
	SEQ ID NO: 444 is a second determined cDNA sequence for clor
30	55153.

		SEQ ID NO: 445 is a first determined cDNA sequence for clone 55154.
		SEQ ID NO: 446 is a second determined cDNA sequence for clone
	55154.	
		SEQ ID NO: 447 is the determined cDNA sequence for clone 55155.
5		SEQ ID NO: 448 is a first determined cDNA sequence for clone 55156.
		SEQ ID NO: 449 is a second determined cDNA sequence for clone
	55156.	
		SEQ ID NO: 450 is a first determined cDNA sequence for clone 55157.
		SEQ ID NO: 451 is a second determined cDNA sequence for clone
10	55157.	
		SEQ ID NO: 452 is the determined cDNA sequence for clone 55158.
		SEQ ID NO: 453 is the determined cDNA sequence for clone 55159.
		SEQ ID NO: 454 is a first determined cDNA sequence for clone 55161.
		SEQ ID NO: 455 is a second determined cDNA sequence for clone
15	55161.	
		SEQ ID NO: 456 is a first determined cDNA sequence for clone 55162.
		SEQ ID NO: 457 is a second determined cDNA sequence for clone
	55162.	
		SEQ ID NO: 458 is a first determined cDNA sequence for clone 55163.
20		SEQ ID NO: 459 is a second determined cDNA sequence for clone
	55163.	
		SEQ ID NO: 460 is a first determined cDNA sequence for clone 55164.
		SEQ ID NO: 461 is a second determined cDNA sequence for clone
	55164.	
25		SEQ ID NO: 462 is a first determined cDNA sequence for clone 55165.
		SEQ ID NO: 463 is a second determined cDNA sequence for clone
	55165.	
	•	SEQ ID NO: 464 is a first determined cDNA sequence for clone 55166.
		SEQ ID NO: 465 is a second determined cDNA sequence for clone
30	55166.	

SEQ ID NO: 466 is a first determined cDNA sequence for clone 55167. SEQ ID NO: 467 is a second determined cDNA sequence for clone 55167. SEQ ID NO: 468 is a first determined cDNA sequence for clone 55168. 5 SEQ ID NO: 469 is a second determined cDNA sequence for clone 55168. SEQ ID NO: 470 is a first determined cDNA sequence for clone 55169. SEQ ID NO: 471 is a second determined cDNA sequence for clone 55169. 10 SEQ ID NO: 472 is a first determined cDNA sequence for clone 55170. SEQ ID NO: 473 is a second determined cDNA sequence for clone 55170. SEQ ID NO: 474 is the determined cDNA sequence for clone 55171. SEQ ID NO: 475 is the determined cDNA sequence for clone 55172. 15 SEQ ID NO: 476 is the determined cDNA sequence for clone 55173. SEQ ID NO: 477 is a first determined cDNA sequence for clone 55174. SEQ ID NO: 478 is a second determined cDNA sequence for clone 55174. SEO ID NO: 479 is the determined cDNA sequence for clone 55175. 20 SEQ ID NO: 480 is the determined cDNA sequence for clone 55176. SEQ ID NO: 481 is the determined cDNA sequence for contig 525. SEQ ID NO: 482 is the determined cDNA sequence for contig 526. SEQ ID NO: 483 is the determined cDNA sequence for contig 527. SEQ ID NO: 484 is the determined cDNA sequence for contig 528. 25 SEQ ID NO: 485 is the determined cDNA sequence for contig 529. SEQ ID NO: 486 is the determined cDNA sequence for contig 530. SEQ ID NO: 487 is the determined cDNA sequence for contig 531. SEQ ID NO: 488 is the determined cDNA sequence for contig 532. SEQ ID NO: 489 is the determined cDNA sequence for contig 533. 30 SEQ ID NO: 490 is the determined cDNA sequence for contig 534.

	SEQ ID NO: 491 is the determined cDNA sequence for contig 535.
	SEQ ID NO: 492 is the determined cDNA sequence for contig 536.
	SEQ ID NO: 493 is the determined cDNA sequence for contig 537.
	SEQ ID NO: 494 is the determined cDNA sequence for contig 538.
5	SEQ ID NO: 495 is the determined cDNA sequence for contig 539.
	SEQ ID NO: 496 is the determined cDNA sequence for contig 540.
	SEQ ID NO: 497 is the determined cDNA sequence for contig 541.
	SEQ ID NO: 498 is the determined cDNA sequence for contig 542.
	SEQ ID NO: 499 is the determined cDNA sequence for contig 543.
10	SEQ ID NO: 500 is the determined cDNA sequence for contig 544.
	SEQ ID NO: 501 is the determined cDNA sequence for contig 545.
	SEQ ID NO: 502 is the determined cDNA sequence for contig 546.
	SEQ ID NO: 503 is the determined cDNA sequence for contig 547.
	SEQ ID NO: 504 is the determined cDNA sequence for contig 548.
15	SEQ ID NO: 505 is the determined cDNA sequence for contig 549.
	SEQ ID NO: 506 is the determined cDNA sequence for contig 550.
	SEQ ID NO: 507 is the determined cDNA sequence for contig 551.
	SEQ ID NO: 508 is the determined cDNA sequence for contig 552.
	SEQ ID NO: 509 is the determined cDNA sequence for contig 553.
20	SEQ ID NO: 510 is the determined cDNA sequence for contig 554.
	SEQ ID NO: 511 is the determined cDNA sequence for contig 555.
	SEQ ID NO: 512 is the determined cDNA sequence for clone 57207
,	SEQ ID NO: 513 is the determined cDNA sequence for clone 57209
	SEQ ID NO: 514 is the determined cDNA sequence for clone 57210
25	SEQ ID NO: 515 is the determined cDNA sequence for clone 57211
	SEQ ID NO: 516 is the determined cDNA sequence for clone 57212
	SEQ ID NO: 517 is the determined cDNA sequence for clone 57213
	SEQ ID NO: 518 is the determined cDNA sequence for clone 57215
	SEQ ID NO: 519 is the determined cDNA sequence for clone 57219
30	SEQ ID NO: 520 is the determined cDNA sequence for clone 57221

SEQ ID NO: 521 is the determined cDNA sequence for clone 57222. SEQ ID NO: 522 is the determined cDNA sequence for clone 57223. SEQ ID NO: 523 is the determined cDNA sequence for clone 57225. SEQ ID NO: 524 is the determined cDNA sequence for clone 57227. 5 SEQ ID NO: 525 is the determined cDNA sequence for clone 57228. SEQ ID NO: 526 is the determined cDNA sequence for clone 57229. SEQ ID NO: 527 is the determined cDNA sequence for clone 57230. SEQ ID NO: 528 is the determined cDNA sequence for clone 57231. SEQ ID NO: 529 is the determined cDNA sequence for clone 57232. 10 SEQ ID NO: 530 is the determined cDNA sequence for clone 57233. SEQ ID NO: 531 is the determined cDNA sequence for clone 57234. SEQ ID NO: 532 is the determined cDNA sequence for clone 57235. SEQ ID NO: 533 is the determined cDNA sequence for clone 57236. SEQ ID NO: 534 is the determined cDNA sequence for clone 57237. 15 SEQ ID NO: 535 is the determined cDNA sequence for clone 57238. SEQ ID NO: 536 is the determined cDNA sequence for clone 57239. SEQ ID NO: 537 is the determined cDNA sequence for clone 57240. SEQ ID NO: 538 is the determined cDNA sequence for clone 57242. SEQ ID NO: 539 is the determined cDNA sequence for clone 57243. 20 SEQ ID NO: 540 is the determined cDNA sequence for clone 57245. SEQ ID NO: 541 is the determined cDNA sequence for clone 57248. SEQ ID NO: 542 is the determined cDNA sequence for clone 57249. SEQ ID NO: 543 is the determined cDNA sequence for clone 57250. SEQ ID NO: 544 is the determined cDNA sequence for clone 57251. 25 SEQ ID NO: 545 is the determined cDNA sequence for clone 57253. SEQ ID NO: 546 is the determined cDNA sequence for clone 57254. SEQ ID NO: 547 is the determined cDNA sequence for clone 57255. SEQ ID NO: 548 is the determined cDNA sequence for clone 57257. SEQ ID NO: 549 is the determined cDNA sequence for clone 57258. 30 SEQ ID NO: 550 is the determined cDNA sequence for clone 57259.

SEQ ID NO: 551 is the determined cDNA sequence for clone 57261. SEQ ID NO: 552 is the determined cDNA sequence for clone 57262. SEQ ID NO: 553 is the determined cDNA sequence for clone 57263. SEQ ID NO: 554 is the determined cDNA sequence for clone 57264. 5 SEQ ID NO: 555 is the determined cDNA sequence for clone 57265. SEQ ID NO: 556 is the determined cDNA sequence for clone 57266. SEQ ID NO: 557 is the determined cDNA sequence for clone 57267. SEQ ID NO: 558 is the determined cDNA sequence for clone 57268. SEQ ID NO: 559 is the determined cDNA sequence for clone 57269. 10 SEQ ID NO: 560 is the determined cDNA sequence for clone 57270. SEQ ID NO: 561 is the determined cDNA sequence for clone 57271. SEQ ID NO: 562 is the determined cDNA sequence for clone 57272. SEQ ID NO: 563 is the determined cDNA sequence for clone 57274. SEQ ID NO: 564 is the determined cDNA sequence for clone 57275. 15 SEQ ID NO: 565 is the determined cDNA sequence for clone 57277. SEQ ID NO: 566 is the determined cDNA sequence for clone 57280. SEQ ID NO: 567 is the determined cDNA sequence for clone 57281. SEQ ID NO: 568 is the determined cDNA sequence for clone 57282. SEQ ID NO: 569 is the determined cDNA sequence for clone 57283. 20 SEQ ID NO: 570 is the determined cDNA sequence for clone 57285. SEQ ID NO: 571 is the determined cDNA sequence for clone 57287. SEQ ID NO: 572 is the determined cDNA sequence for clone 57288. SEQ ID NO: 573 is the determined cDNA sequence for clone 57289. SEQ ID NO: 574 is the determined cDNA sequence for clone 57290. 25 SEQ ID NO: 575 is the determined cDNA sequence for clone 57292. SEQ ID NO: 576 is the determined cDNA sequence for clone 57295. SEQ ID NO: 577 is the determined cDNA sequence for clone 57296. SEQ ID NO: 578 is the determined cDNA sequence for clone 57297. SEQ ID NO: 579 is the determined cDNA sequence for clone 57299. 30 SEQ ID NO: 580 is the determined cDNA sequence for clone 57301.

SEQ ID NO: 581 is the determined cDNA sequence for clone 57302.

SEQ ID NO: 582 is the determined cDNA sequence for the beta chain of a lung tumor specific T cell receptor.

SEQ ID NO: 583 is the determined cDNA sequence for the alpha chain of a lung tumor specific T cell receptor.

SEQ ID NO: 584 is the amino acid sequence encoded by SEQ ID NO:

SEQ ID NO: 585 is the amino acid sequence encoded by SEQ ID NO: 582.

SEQ ID NO: 586 is the amino acid sequence encoded by the 5' terminus of 14F10.

SEQ ID NO: 587 is the amino acid sequence of a T cell epitope contained within SEQ ID NO: 586.

### DETAILED DESCRIPTION OF THE INVENTION

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The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly lung cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (e.g., T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B.

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Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

### Polypeptide Compositions

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As used herein, the term "polypeptide" is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583. Certain other illustrative polypeptides of the invention comprise amino acid sequences as set forth in any one of SEQ ID NOs: 391, 393, 395, 397, 421, 425-427, 434-439 and 584-587.

The polypeptides of the present invention are sometimes herein referred to as lung tumor proteins or lung tumor polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in lung tumor samples. Thus, a "lung tumor polypeptide" or "lung tumor protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of lung tumor samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of lung tumor samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal tissues, as determined using a representative assay provided herein. A lung tumor polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with lung cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one illustrative example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide. Immunogenic portions may generally be identified using well known techniques, such

as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that is not substantially less than the reactivity of the full-length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, e.g., having greater than about 100% or 150% or more immunogenic activity.

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In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other illustrative immunogenic portions will contain a small N-and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or

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one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide compositions set forth herein, such as those set forth in SEQ ID NOs: 391, 393, 395, 397, 421, 425-427, 434-439 and 584-587, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provide by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set for the herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic

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activity as described herein and/or using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

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For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

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TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU		,		
Glutamic acid	Glu	E	GAA	GAG	-			
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	√GGÙ		
Histidine	His	$\mathbf{H}$	CAC	CAU				
Isoleucine	Įle	1	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	-CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	-CCU		
Glutamine	Gln	·Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	·CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	Ť	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU			····	

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its

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hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

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It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine ( $\pm$ 3.0); lysine ( $\pm$ 3.0); aspartate ( $\pm$ 3.0  $\pm$  1); glutamate ( $\pm$ 3.0  $\pm$  1); serine ( $\pm$ 0.3); asparagine ( $\pm$ 0.2); glutamine ( $\pm$ 0.2); glycine (0); threonine ( $\pm$ 0.4); proline ( $\pm$ 0.5  $\pm$ 1); alanine ( $\pm$ 0.5); histidine ( $\pm$ 0.5); cysteine ( $\pm$ 1.0); methionine ( $\pm$ 1.3); valine ( $\pm$ 1.5); leucine ( $\pm$ 1.8); isoleucine ( $\pm$ 1.8); tyrosine ( $\pm$ 2.3); phenylalanine ( $\pm$ 2.5); tryptophan ( $\pm$ 3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm$ 2 is preferred, those within  $\pm$ 1 are particularly preferred, and those within  $\pm$ 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that

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take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetylmethyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

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Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the

polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

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Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these

algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

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In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion 30 polypeptide that comprises multiple polypeptides as described herein, or that comprises

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at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as

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linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

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The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a Mycobacterium sp., such as a Mycobacterium tuberculosis-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the

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purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein 30 known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is

derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

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Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4<sup>+</sup> T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

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In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, e.g., are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

## Polynucleotide Compositions

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The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the

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present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably and immunogenic variant or derivative, of such a sequence.

Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

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In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440-583, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide sequence of this invention using the methods described herein, (e.g., BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth

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herein). The term "variants" should also be understood to encompasses homologous genes of xenogenic origin.

additional embodiments, present invention provides the In polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; including all integers through 200-500; 500-1,000, and the like.

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In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of For purposes of illustration, suitable moderately stringent molecular biology. conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, e.g., to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, 30 *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides

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that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

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When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.

In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

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One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments;

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or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis 30 approach, such as site-specific mutagenesis, is employed for the preparation of

immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

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In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

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As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically,

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vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, e.g., those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, e.g., Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the

complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having genecomplementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

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Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR<sup>TM</sup> technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

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Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine

type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

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Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothicated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T<sub>m</sub>, binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection

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considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997, 25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

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According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs

through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

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The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead.

1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada et al., Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

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Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by

incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

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Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells Ribozymes expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, Antisense Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in

techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen et al., Science 1991 Dec 6;254(5037):1497-500; Hanvey et al., Science 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, Bioorg Med Chem. 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

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PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography,

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providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton et al., Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen et al., J Pept Sci. 1995 May-Jun;1(3):175-83; Orum et al., Biotechniques. 1995 Sep;19(3):472-80; Footer et al., Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith et al., Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge et al., Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa et al., Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini et al., Blood. 1996 Aug 15;88(4):1411-7; Armitage et al., Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger et al., Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore<sup>TM</sup> technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of

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transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

## Polynucleotide Identification, Characterization and Expression

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Polynucleotides compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR<sup>TM</sup>) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR<sup>TM</sup>, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (e.g., Taq polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse

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transcription and PCR<sup>TM</sup> amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR TM amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or

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bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

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Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl.

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Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

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As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction

sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

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Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences 30 encoding the polypeptide, or functional equivalents, may be inserted into appropriate

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expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

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A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector-enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains

multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional E. coli cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) J. Biol. Chem. 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

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In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol*. 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991)

Results Probl. Cell Differ. 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci. 91*:3224-3227).

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In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion

thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

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For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or

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aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies

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specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

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Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are

not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif. 3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol. 12*:441-453).

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In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

## Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunogically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an

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ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant  $(K_d)$  of the interaction, wherein a smaller  $K_d$  represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant"  $(K_{on})$  and the "off rate constant"  $(K_{off})$  can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of  $K_{off}/K_{on}$  enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant  $K_d$ . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

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An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen,

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and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

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Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a

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superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

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Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and

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extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')<sub>2</sub>" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V<sub>H</sub>::V<sub>L</sub> heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

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A single chain Fv ("sFv") polypeptide is a covalently linked  $V_H$ :: $V_L$  heterodimer which is expressed from a gene fusion including  $V_H$ - and  $V_L$ -encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, e.g., U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-

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terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

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As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) Nature 349:293-299; Lobuglio et al. (1989) Proc. Nat. Acad. Sci. USA 86:4220-4224; Shaw et al. (1987) J Immunol. 138:4534-4538; and Brown et al. (1987) Cancer Res. 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) Nature 332:323-327; Verhoeyen et al. (1988) Science

239:1534-1536; and Jones et al. (1986) Nature 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, e.g., a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) Ann. Rev. Biochem. 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (e.g., solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable

domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (e.g., electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

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In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a

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substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.

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Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

# T Cell Compositions

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The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex<sup>TM</sup> System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide.

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Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

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T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a

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variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

## Pharmaceutical Compositions

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In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, e.g., other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and theraputic vaccine applications. Vaccine preparation is generally described in, for example, M.F.

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Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

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In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S.

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Pat. No. 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-990; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-852; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-8037; and Boris-Lawrie and Temin (1993) Cur. Opin. Genet. Develop. 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) J. Virol. 57:267-274; Bett et al. (1993) J. Virol. 67:5911-5921; Mittereder et al. (1994) Human Gene Therapy 5:717-729; Seth et al. (1994) J. Virol. 68:933-940; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-629; and Rich et al. (1993) Human Gene Therapy 4:461-476).

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Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) Molec. Cell. Biol. 8:3988-3996; Vincent et al. (1990) Vaccines 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) Current Opinion in Biotechnology 3:533-539; Muzyczka, N. (1992) Current Topics in Microbiol. and Immunol. 158:97-129; Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene

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encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, e.g., Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, e.g., WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based

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on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. J. Biol. Chem. (1993) 268:6866-6869 and Wagner et al. Proc. Natl. Acad. Sci. USA (1992) 89:6099-6103, can also be used for gene delivery under the invention.

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Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in the specific location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK) and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device, propelling the particles into a target tissue of interest.

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In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous One preferred type of immunostimulant comprises an adjuvant. antigen. adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes;

biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

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Within certain embodiments of the invention, the adjuvant composition is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL® adjuvants are available from Corixa Corporation (Seattle, WA; see, for example, US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or Gypsophila or Chenopodium quinoa saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example

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combinations of at least two of the following group comprising QS21, QS7, Quil A,  $\beta$ -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamelar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol<sup>R</sup> to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

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In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL® adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-MPL® adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart,

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Belgium), Detox (Enhanzyn®) (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula

(I):  $HO(CH_2CH_2O)_n$ -A-R,

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wherein, n is 1-50, A is a bond or -C(O)-, R is  $C_{1-50}$  alkyl or Phenyl  $C_{1-50}$  alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein n is between 1 and 50, preferably 4-24, most preferably 9; the R component is  $C_{1-50}$ , preferably  $C_4$ - $C_{20}$  alkyl and most preferably  $C_{12}$  alkyl, and A is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-steoryl ether, polyoxyethylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12<sup>th</sup> edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or

maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

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Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

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APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the

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present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (e.g., a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (see e.g., U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

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In another illustrative embodiment, biodegradable microspheres (e.g., polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems. such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further 30 comprise one or more buffers (e.g., neutral buffered saline or phosphate buffered

saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

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The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including e.g., oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia,

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cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

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Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

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In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

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Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, The carrier can be a solvent or dispersion medium such as bacteria and fungi. containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, 30 the solution should be suitably buffered if necessary and the liquid diluent first rendered

isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

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In another embodiment of the invention, the compositions disclosed formulated in neutral salt form. herein be a or Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase

"pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs via nasal aerosol sprays has been described, e.g., in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga et al., J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

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The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998 Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery

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systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, he use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs).

Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero et al., Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 µm) may be designed using polymers able to be degraded in vivo. Such particles can be made as described, for example, by Couvreur et al., Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen et al., Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux et al. J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

## Cancer Therapeutic Methods

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20 In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of lung cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the

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pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

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Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumorinfiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokineactivated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for

immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

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Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccinedependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or

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partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

# 15 Cancer Detection and Diagnostic Compositions, Methods and Kits

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In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory,

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1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

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In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and

functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

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In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The

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immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

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The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, 30 the signal detected from the reporter group that remains bound to the solid support is

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generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site

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generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

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A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells,

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activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

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As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably. oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

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One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

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In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor.

One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in

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optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

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Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

#### **EXAMPLE 1**

# PREPARATION OF LUNG TUMOR-SPECIFIC CDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a (dT)<sub>12</sub>AG (SEQ ID NO: 47)

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anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM MgCl<sub>2</sub>, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

15 EXAMPLE 2

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# USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco

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BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 - LT86-8 and LT86-10 - LT86-15 are 5 provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the corresponding predicted amino acid sequences from the 3' and 5' ends 10 being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 - LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-15 15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some homology with a C. elegans leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence 20 showing homology to the previously identified antisense sequence of interferon alphainduced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 25 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA

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sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

In further studies, a cDNA expression library was prepared using mRNA from a lung small cell carcinoma cell line in the lambda ZAP Express expression vector (Stratagene), and screened as described above, with a pool of two lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Seventy-three clones were isolated. The determined cDNA sequences of these clones are provided in SEQ ID NO: 290-362. The sequences of SEQ ID NO: 289-292, 294, 296-297, 300, 302, 303, 305, 307-315, 317-320, 322-325, 327-332, 334, 335, 338-341, 343-352, 354-358, 360 and 362 were found to show some homology to previously isolated genes. The sequences of SEQ ID NO: 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 were found to show some homology to previously identified ESTs.

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# **EXAMPLE 3**

# Use Of Mouse Antisera To Identify Dna Sequences Encoding Lung Tumor Antigens

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using

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a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

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provided in SEQ ID NO: 81-83.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

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In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology to previously identified human polynucleotide sequences.

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### **EXAMPLE 4**

# USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage

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was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for -expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences 5 for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEO ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

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Using the procedures described above, two directional cDNA libraries 20 (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). 25 Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences

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of SEQ ID NO: 217, 223, 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254, 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

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The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in normal tissues was determined by microarray technology. The results of these studies are shown below in Table 2, together with the databank analyses for these sequences.

TABLE 2

Clone	SEQ ID NO:	Description	LT+F/N	SCC+M/N	Squa/ N	Adeno/N
2LT-3	238	Unknown (KIAA0712)	2.2	3.8	3.3	_
2LT-6	239	Lactate DH B	2.3	3.8	4.1	-
2LT-22	240	Fumarate hydratase	-	3.0	-	-
2LT-26	242	CG1-39	-	-	12.8	-
2LT-31	243	ADH7		-	8.4	2.2
2LT-36	244	ADH7	-	2.4	2.0	-
2LT-42	245	HMG-CoA synthase	2.2	2.6	2.2	-
2LT-54	247	(Mus) ninein	_	2.1	-	-
2LT-55	248	Ubiquitin	2.2	_	2.5	2.0
2LT-57	249	Novel	2.1	2.9	2.4	-

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2LT-58	250	Novel	2.3	4.0	2.9	-
2LT-59	251	Unknown KIAA0784	2.4	3.0	2.3	2.0
2LT_62	252	Nuc Pore Cmplx- ass pro TPR	-	-	_	2.1
2LT-70	256	Unknown KIAA0871	_	2.5	2.2	2.1
2LT-73	257	Mus polyadenylate- binding	-	2.0	-	•
2LT-76	259	Trans-Golgi p230	2.1	-	2.6	-
2LT-85	263	Ribosomal protein (LS29)	-	Pea .	-	2.1
2LT-89	265	Unknown PAC212G6	-	2.0	_	_
2LT-98	268	Melanoma diff assoc pro 9	-	••	_	2.2
2LT-100	269	Mus Collagen alpha VI	-	-	-	2.1
2LT-105	271	NY-CO-7 antigen	-	3.2	-	_
2LT-108	273	Unknown RG363M04	-	3.1	•••	, <del>-</del>
2LT-124	279	Galectin-9 (secreted)	2.3	2.7	2.0	-
2LT-126	280	L1 element L1.33 p40	2.5	-	3.1	-
2LT-128	282	Novel (kappa B- ras 2)	2.3+	-	20.4	2.5
2LT-133	284	alpha II spectrin	-	2.3	-	-

LT+F/N = Lung Tumor plus Fetal tissue over Normal tissues

SC+M/N = Lung Small Cell carcinoma plus Metastatic over Normal tissues

Squa/N = Squamous lung tumor over Normal tissues

5 Aden/N = Adenocarcinoma over Normal tissues

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Full-length sequencing studies on antigen 2LT-128 (SEQ ID NO: 282) resulted in the isolation of the full-length cDNA sequence provided in SEQ ID NO: 392. This amino acid sequence encoded by this full-length cDNA sequence is provided in SEQ ID NO: 393. This antigen shows 20-fold over-expression in squamous cell carcinoma and 2.5-fold over-expression in lung adenocarcinoma. This gene has been described as a potential ras oncogene (Fenwick et al. *Science*, 287:869-873, 2000).

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Extended sequence information was obtained for clones 2LT-3 (SEQ ID NO:238), 2LT-26 (SEQ ID NO:242), 2LT-57 (SEQ ID NO: 249), 2LT-58 (SEQ ID NO:250), 2LT-98 (SEQ ID NO:268) and 2LT-124 (SEQ ID NO:279). The extended cDNA sequences for these clones are set forth in SEQ ID NOs:428-433, respectively, encoding the polypeptide sequences set forth in SEQ ID NOs: 434-439, respectively.

### EXAMPLE 5

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DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using 10 RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42°C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. 1  $\mu$ l of 1:30 dilution of cDNA was employed to enable the linear range amplification of the  $\beta$ -actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor, colon tumor and lung tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues

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tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

5 EXAMPLE 6

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ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 Curr. Opin. Oncol. 9:79-87; Okamoto, K. et al. 1996 Int. J. Cancer 65:437-41; Wu, C. et al. 1995 Biochem. Biophys. Res. Commun. 30 214:1239-45; Porter, D.W. et al. 1996 Chem. Res. Toxicol. 9:1375-81). SLT-T1 may

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thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

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The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

cDNA sequences encoding antigens potentially involved in small cell lung carcinoma development were isolated as follows. cDNA expression libraries were constructed with mRNA from the small cell lung carcinoma cell lines NCIH69, NCIH128 and DMS79 (all available from the American Type Culture Collection, Manassas, VA) employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Phagemid were rescued at random and the cDNA sequences of 27 isolated clones were determined. Comparison of the determined cDNA sequences revealed no significant homologies to the sequences of SEQ ID NO: 372 and 373. The sequences of SEQ ID NO: 364, 369, 377, 379 and 386 showed some homology to previously isolated ESTs. The sequences of the remaining 20 clones showed some homology to previously identified genes. The cDNA sequences of these clones are provided in SEQ ID NO:

363, 365-368, 370, 371, 374-376, 378, 380-385 and 387-389, wherein SEQ ID NO: 363, 366-368, 370, 375, 376, 378, 380-382, 384 and 385 are full-length sequences.

Comparison of the cDNA sequence of SEQ ID NO: 372 indicated that this clone (referred to as 128T1) is a novel member of a family of putative seven pass transmembrane proteins. Specifically, using the computer algorithm PSORT, the protein was predicted to be a type IIIA plasma membrane seven pass transmembrane protein. A genomic clone was identified in the Genbank database which contained the predicted N-terminal 58 amino acids missing from the amino acid sequence encoded by SEQ ID NO: 372. The determined full-length cDNA sequence for the 128T1 clone is provided in SEQ ID NO: 390, with the corresponding amino acid sequence being provided in SEQ ID NO: 391.

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The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in normal tissues was determined by microarray technology. The results of these studies are shown below in Table 3, together with the databank analyses for these sequences.

TABLE 3

Clone	SEQ ID NO:	Description	LT+F/N	SCC+M/N	Squa/ N	Adeno/N
DMS79- T1	363	STAT-ind inhib of cytokine	. =	2.0	noù	-
DMS79- T6	367	Neuronal cell death related	-	2.2	_ `	-
DMS79- T9	369	Novel	-	2.2	-	-
DMS79- T10	370	Ubiquitin carrier protein	_	3.9	2.2	-
DMS79- T11	371	HPV16E1 pro binding protein	-	2.1	-	-
128-T9	378	Elongation factor 1	***	2.7	-	-
128T11	380	Malate dehyrogenase	-	2.3	2.0	-
128-T12	381	Apurinic/apyrim endonuclease	-	5.4	-	-
NCIH69-	382	Sm-like protein	-	-	2.4	-

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T3		CaSm			
NCIH69-	384	Transcription	-	2.5	 _
Т6		factor BTF3a			

LT+F/N = Lung Tumor plus Fetal tissue over Normal tissues

SC+M/N = Lung Small Cell carcinoma plus Metastatic over Normal tissues

Squa/N = Squamous lung tumor over Normal tissues

5 Aden/N = Adenocarcinoma over Normal tissues

### **EXAMPLE 7**

### SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-10 Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol 15 (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types 20 of mass spectrometry and by amino acid analysis.

## **EXAMPLE 8**

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG TUMOR
ANTIGENS BY T-CELL EXPRESSION CLONING

Lung tumor antigens may also be identified by T cell expression cloning.

One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the 75%/HBSS interface contained predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8+ T cells (>90% of gated population) with only a small percentage of CD4+ cells.

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In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line (referred to as LT391-06), which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS analysis to confirm high expression levels of CD80, class I MHC and class II MHC molecules.

The ability of the TIL lines to specifically recognize autologous lung tumor was demonstrated by cytokine release assays (IFN-γ and TNF-α) as well as <sup>51</sup>Cr release assays. Briefly, TIL cells from day 21 cultures were co-cultured with either autologous or allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-

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2. Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. The specificity of these clones for autologous tumor was confirmed by <sup>51</sup>Cr microcytotoxicity and IFN-γ bioassays.

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These CTL clones were demonstrated to be HLA-B/C restricted by antibody blocking experiments. A representative CTL clone was tested on a panel of allogeneic lung carcinomas and it recognized both autologous tumor and a lung squamous cell carcinoma (936T). As the only class I MHC molecule shared among these tumors was HLA-Cw1203, this indicated that this was the restriction element used by the CTL. This finding was confirmed by the recognition of a number of allogeneic lung carcinomas transduced with a retroviral vector encoding HLA-Cw1203 by the CTL.

PolyA mRNA was prepared from a lung tumor cell line referred to as LT391-06 using Message Maker (Life Technologies; Rockville, MD). The subsequent steps involving cDNA synthesis were performed according to Life Technologies cloning manual (SuperScript Plasmid System for cDNA Synthesis and Plasmid Cloning). Modifications to the protocol were made as follows. At the adapter addition step, EcoRI-XmnI adapters (New England Biolabs; Beverly, MA) were substituted. Size fractionated cDNAs were ligated into the expression vector system HisMax A, B, C (Invitrogen; Carlsbad, CA) to optimize for protein expression in all three coding frames. Library plasmids were then aliquotted at approximately 100 CFU/well into a 96-well block for overnight liquid amplification. From these cultures, glycerol stocks were made and pooled plasmid was prepared by automated robot (Qiagen; Valencia, CA). The concentration of the plasmid DNA in each well of the library plates was determined to be approximately 150 ng/ul. Initial characterization of the cDNA expression library was performed by randomly sequencing 24 primary transformants and subjecting the resulting sequences to BLAST searches against available databases.

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The determined cDNA sequences are provided in SEQ ID NO: 443-480, with the results of the BLAST searches being provided in Table 4.

TABLE 4

Clone	SEQ ID NO:	GenBank Accession	Description
55163	458, 459	Accession	Novel in Genbank
55158	452	<del></del>	Novel in Genbank
		quences with u	nknown function
	o <b>e</b> ) oo maan a	1 22 4 5 4 5 4 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
55153	443, 444	7018516	H. sapiens mRNA; cDNA DKFZp434M035
55154	445, 446	6437562	H. sapiens Chr 22q11 PAC Clone p393
55157	450, 451	2887408	H. sapiens KIAA0417 mRNA
55165	462, 463	3970871	H. sapiens HRIHFB2122 mRNA
Homol	ogy to known se	quences with ki	nown function
55155	447	7677405	H. sapiens F-box protein FBS (FBS)
55156	448, 449	3929584	H. sapiens EEN pseudogene
55161	454, 455	4503350	H. sapiens DNA (cytosine-5-)-
7.1.50			methyltransferase 1 (DNMT1)
55162	456, 457	31220	ERK1 mRNA for protein serine/threonine
55164	460 461	((77)	kinase
55164	460, 461	6677666	H. sapiens RNA-binding protein (autoantigenic) (RALY)
55166	464, 465	3249540	H. sapiens ribonuclease P protein subunit
33100	707, 402	3249340	p40 (RPP40)
55167	466, 467	7657497	H. sapiens renal tumor antigen (RAGE)
55168	468, 469	2873376	H. sapiens exportin t mRNA
55169	470,471	3135472	H. sapiens Cre binding protein-like 2
			mRNA
55171	474	4759151	H. sapiens spermine synthase (SMS)
55173	476	6688148	H. sapiens partial mRNA for NICE-3
			protein
55174	477, 478	531394	Human transcriptional coactivator PC4
55175	479	6563201	H. sapiens translation initiation factor eIF-
			2b delta subunit
55176	480	29860	hCENP-Bgene, for centromere autoantigen
			B (CENP-B)
	ogy to Ribosoma		
55159	453	337494	Ribosomal protein L7a (surf 3) large subunit mRNA
55170	472, 473	4506648	H.sapiens mRNA for ribosomal protein L3

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Clone	SEQ ID NO:	GenBank Accession	Description
55172	475	388031	H. sapiens ribosomal protein L11

For T cell screening, approximately 80 ng of the library plasmid DNA and 80 ng of HLA-Cw1203 plasmid DNA was mixed with the lipid Fugene according to the manufacturers' instructions and transfected in duplicate into COS-7 cells. After incubation at 37 °C for 48 hours, the transfection mixture was removed and 10,000 LT391-06 CTL were added to each well in fresh media containing human serum.

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The ability of T cells to recognize an antigen in the library was assessed by cytokine release after 6 hours (TNF-alpha, WEHI bio-assay) or after 24 hours (IFN-gamma, ELISA). Approximately 2.0 x 10<sup>5</sup> clones (in plasmid pools of 100) were screened using this system in COS-7 cells. Three plasmid pools were identified (referred to as 14F10, 19A4, and 20E10) that were recognized by LT391-06 CTL. Transfection of these plasmid pools into COS-7 cells led to production of both IFN-gamma and TNF-alpha from the LT391-06 CTL at levels significantly above background. Pools 14F10, 19A4 and 20E10 were "broken down" into several hundred individual plasmid DNAs and retested. The sequences of 24 novel clones isolated from pool 14F10 are provided in SEQ ID NO: 481-511.

One plasmid (3D9) from pool 14F10, one plasmid from pool 20E10 and 5 plasmids (2A6, 2E11, 2F12, 3F4, 3H8) from pool 19A4 were capable of reconstituting T cell recognition. Sequencing of these plasmids led to the identification of a 7.8 kB cDNA insert (referred to as clone 14F10), a 2.2 kB cDNA insert (referred to as clone 19A4; SEQ ID NO:440), and a clone referred to as 20E10. The full-length cDNA sequence for 14F10 is provided in SEQ ID NO: 441. Clone 14F10 does not contain the first two "G" nucleotides found at the 5' end of 19A4, and the 3'-proximal 24 bp of 19A4 differ from the corresponding region of 14F10 (nucleotides 2145-2165). Furthermore, 3837 bp of 3' additional sequence was isolated for clone 14F10. The 5' terminal cDNA sequence (337 bp) of clone 20E10 is provided in SEQ ID NO: 442. 20E10 contains an additional 3 nucleotides (as compared to 19A4) at the 5'-most end. The additional sequence from the 5' end of clone 20E10 contains an "ATG" and

therefore appears to contain the translational start site of a novel open reading frame. BLAST search analysis against the GenBank database identified these sequences as having significant homology with a truncated human cystine/glutamate transporter gene. Unlike the published sequence, however, clones 14F10 and 19A4 contain a unique 5' terminus consisting of 181 nucleotides. This novel sequence replaces the published 5' region and results in the removal of the reported initiating methionine (start codon) and an additional two amino acids of the reported transporter protein. Therefore, the translated product of clones 14F10 and 19A4 is different than the cystine/glutamate transporter protein. Furthermore, T cell recognition of other lung tumors demonstrates that this antigen is expressed by other tumors as well.

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The epitope and amino acid sequence encoded within clones 19A4 and 14F10 which reconstitutes T cell recognition of anti-LT391-06 cells were mapped as follows. Cos-7 cells were transfected with 80 ng/well HLA-Cw1203 along with titrated amounts of cDNA encoding clone 19A4, a potential open reading frame located in the unique 5' terminus of 19A4, or the open reading frame from the cystine/glutamate (Cys-Glu) transporter gene, cloned into a eukaryotic expression vector and tested for stimulation of anti-LT391-06 T cells in a TNF assay. As a positive control Cos-7 cells were co-transfected with HLA-Cw1203 and the positive plasmid clone 19A4 described above. The Cys-Glu transporter expression construct was isolated by PCR using 5' and 3' primers specific for the known ORF of the transporter with 19A4 as template. In addition, each 5' primer contained a Kozak translation initiation site and starting methionine to drive translation of the polypeptide. CTL against LT391-06 did not recognize transfectants expressing 19A4 and the 5' ORF from 19A4.

In subsequent experiments, Cos-7 cells were co-transfected with 80 ng/well HLA-Cw1203 along with titrated amounts of DNA of transposition mutants F10 and C12, respectively, and tested for simulation of anti-LT391-06 T cells in a TNF assay. As a positive control, Cos-7 cells were co-transfected with HLA-Cw1203 and clones of the 5' ORF of 19A4. Transposition mutants F10 and C12 were obtained by transposon-mediated mutation of the 14F10 clone and screening for insertion site by

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sequence analyses. The transposon of mutant F10 is inserted approximately 304 bp from the 5' EcoRI cloning site of the 14F10 cDNA. This mutation did not disrupt translation of the T cell epitope. By contrast, the transposon of mutant C12, which is inserted approximately 116 bp from the 5' EcoRI cloning site of the 14F10 cDNA, was found to interrupt translation of the T cell epitope. Thus the epitope in 14F10 maps between these two transposon insertion sites. The amino acid sequence of the region between the C12 and F10 transposon insertion sites is provided in SEQ ID NO: 586.

A series of 11 overlapping 16-mer and 15-mer peptides for the region shown in SEQ ID NO: 586 were prepared and tested for stimulation of anti-LT391-06 cells, as determined by cytokine release in TNF and IFN-γ assays. Only the peptide provided in SEQ ID NO: 587 (corresponding to residues 5-20 of SEQ ID NO: 586) stimulated cytokine release. These studies demonstrate that the HLA-Cw1203 restricted epitope of the LT391-06 antigen is contained within SEQ ID NO: 587.

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### **EXAMPLE 9**

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING
LUNG TUMOR ANTIGENS BY PCR SUBTRACTION

This example describes the isolation and characterization of cDNA clones from a PCR subtracted expression library prepared from the human lung tumor cell line LT391-06 described above.

Tester poly A mRNA was prepared from the cell line LT391-06 as described above. Driver poly A mRNA was isolated from a human acute T cell leukemia/T lymphocyte cell line (Jurkat) which is derived from non-lung cells and is not recognized by LT391-06 reactive T cells. The subtraction was performed according to the method of Clontech (Palo Alto, CA) with the following changes: 1) a second restriction digestion reaction of cDNA was completed using a pool of enzymes (MscI, PvuII, StuI and DraI). This was in addition to, and separate from, the Clontech recommended single restriction enzyme digestion with RsaI. Each restriction digest set was treated as a separate library to ensure that the final mixed library contained overlapping fragments. Thus, the epitope recognized by the T cells should be represented on a fragment within the library and not destroyed by the presence of a

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single restriction site within it. 2) The ratio of driver to tester cDNA was increased in the hybridization steps to increase subtraction stringency. To analyze the efficiency of the subtraction, actin was PCR amplified from dilutions of subtracted, as well as unsubtracted, PCR samples. The second amplification step utilized primers that were modified from those normally used. Three nested PCR primers were engineered to contain a cleavable EcoRI site (not utilized during cloning) that was in one of three frames. Thus, secondary amplification with these primers resulted in products that could be ligated directly into the eukaryotic expression plasmid pcDNA4His/Max-Topo This resulted in the PCR subtracted and amplified fragments being (Invitrogen). represented in-frame somewhere within the library. Due to the mechanics of the subtraction only 50% of fragments will be in the correct orientation. The complexity and redundancy of the library was characterized by sequencing 96 randomly picked clones from the final pooled PCR subtraction expression library, referred to as LT391-06PCR. These sequences (SEQ ID NO: 512-581) were analyzed by comparison to sequences in publicly available databases (Table 5).

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TABLE 5

Clone	SEQ ID NO:	GenBank Accession	Description
57235	532		Novel in Genbank
57255	547		Novel in Genbank
57264	554		Novel in Genbank
Homol	ogy to known se	quences with u	nknown function
57215	518	5689540	H. sapiens mRNA for KIAA1102 protein
57223	522	2341006	Human Xq13 3' end of PAC 92E23
57227	524	7022540	H. sapiens cDNA FLJ10480 fis, clone NT2RP2000126
57238	535	6807795	H. sapiens mRNA; cDNA DKFZp761G02121
57239	536	5757546	H. sapiens clone DJ0823F17
57243	539	7023805	H. sapiens cDNA FLJ11259 fis, clone PLACE1009045
57245	540	4884472	H. sapiens mRNA; cDNA DKFZp586O2223
57267	557	6808218	H. sapiens mRNA; cDNA DKFZp434O1519
57268	558	10040400	Sequence 12 from Patent WO9954460

Clone	SEQ ID NO:	GenBank	Description Description					
		Accession	77.					
57270	560	7959775	H. sapiens PRO1489 mRNA					
57271	561	4500158	H. sapiens mRNA; cDNA DKFZp586B0918					
57281	567	6560920	H. sapiens clone RP11-50107					
57283	569	285962	Human mRNA for KIAA0108 gene					
57285	570	7019813	H, sapiens cDNA FLJ20002 fis, clone					
		,	ADKA01577					
Homol	Homology to known sequences with known function							
57207	512	517176	H. sapiens YAP65 mRNA					
57210	514	6841233	H. sapiens HSPC292 mRNA					
57211	515	2606093	H. sapiens Cyr61 protein (CYR61) mRNA					
57212	516	339648	Human thioredoxin (TXN) mRNA					
57219	519	4504616	H. sapiens insulin- like growth factor binding protein 3 (IGFBP3)					
57221	520	7274241	H. sapiens novel retinal pigment epithelial cell protein (NORPEG)					
57222	521	189564	Human, plasminogen activator inhibitor- 1 gene					
57228	525	4757755	H. sapiens annexin A2 (ANXA2)					
57230	527	180800	Human alpha- 1 collagen type IV gene, exon 52					
57232	529	6729061	H. sapiens clone RPC11- 98D12 from 7q31					
57233	530	338391	Spermidine/ spermine N1- acetyltransferase					
57234	531	7305302	H. sapiens NCK- associated protein 1 (NCKAP1)					
57236	533	4929722	H. sapiens CGI- 127 protein					
57242	538	4503558	H. sapiens epithelial membrane protein 1 (EMP1)					
57248	541	183585	Human pregnancy- specific beta- glycoprotein c					
57250	543	4759283	H. sapiens ubiquitin carboxyl- terminal esterase L1 (UCHL1)					
57251	544	1236321	Human laminin gamma2 chain gene (LAMC2)					
57253	545	213831	H. sapiens lysyl hydroxylase isoform 2 (PLOD2)					
57254	546	536897	Human follistatin- related protein precursor mRNA					
57257	548	339656	Human endothelial cell thrombomodulin					
57258	549	190467	Human prion protein (PrP) mRNA					
57261	551	338031	Human serglycin gene					
57262	552	178430	Human alphoid DNA (alphoid repetitive					

Clone	SEQ ID NO:	GenBank Accession	Description
		,	sequence)
57265	555	4502562	H. sapiens calpain, large polypeptide L2 (CAPN2)
57266	556	398163	H. sapiens mRNA for insulin- like growth factor binding protein- 3
57269	559	7262375	H. carboxylesterase 2 (intestine, liver) (CES2)
57272	562	467560	H. sapiens mRNA for cysteine dioxygenase type 1
57274	563	482664	H. sapiens annexin A3 (ANXA3)
57275	564:	2281904	H. sapiens Bruton's tyr. kinase (BTK), alpha- D- galactosidase A (GLA)
57277	565	4557498	H. sapiens C- terminal binding protein 2 (CTBP2)
57282	568	189245	Human, NAD(P) H: menadione oxidoreductase mRNA
57287	571	28525	Human mRNA for amyloid A4 precursor of Alzheimer's disease
57288	572	4757755	H. sapiens annexin A2 (ANXA2)
57289	573	5729841	H. sapiens glyoxalase I (GLO1) mRNA
57290	574	6103642	H. sapiens F- box protein FBX3 mRNA
57295	576	182513	Human ferritin L chain mRNA
57299	579	37137	Human mRNA for thrombospondin
57301	580	179682	Human (clone A12) C4b- binding protein beta- chain
57302	581	6042205	H. sapiens membrane metallo- endopeptidase (neutral endopeptidase, enkephalinase, CALLA, CD10) (MME)
57213	517	2665791	H. sapiens caveolin- 2 mRNA
57259	550	2665791	H. sapiens caveolin- 2 mRNA
57225	523	179765	Human calcyclin gene
57229	526	179765	Human calcyclin gene
57237	534	186962	Human laminin B2 chain gene
57249	542	186962	Human laminin B2 chain gene
57231	528	4972626	H. sapiens caveolin 1 (CAV1) gene
57296	577	4972626	H. sapiens caveolin 1 (CAV1) gene
57297	578	4972626	H. sapiens caveolin 1 (CAV1) gene
57240	537	266237	insulin- like growth factor binding protein 3
57292	575	184522	Human insulin- like growth factor- binding protein- 3 gene
57263	553	4504618	H. sapiens insulin- like growth factor

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Clone	SEQ ID NO:	GenBank Accession	Description
		,	binding protein 7 (IGFBP7)
57280	566	4504618	H. sapiens insulin- like growth factor binding protein 7 (IGFBP7)
Homol	ogy to Ribosoma	l Protein	
57209	513	337504	Human ribosomal protein S24 mRNA

#### EXAMPLE 10

# ISOLATION AND CHARACTERIZATION OF T CELL RECEPTORS FROM T CELL CLONES SPECIFIC FOR LUNG TUMOR ANTIGENS

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This example describes the cloning and sequencing of T cell receptor (TCR) alpha and beta chains from a CD8 T cell clone specific for an antigen expressed by the lung tumor cell line LT391-06. T cells have a limited lifespan. Cloning of TCR chains and subsequent transfer would essentially enable infinite propagation of the T cell specificity. Cloning of tumor antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share TCR MHC-restricting alleles. Such T cells can then be expanded and used in adoptive transfer techniques to introduce the tumor antigen specificity into patients carrying tumors that express the antigen (see, for example, Clay et al. *J. Immunol.* 163:507 (1999)).

Cytotoxic T lymphocyte (CTL) clones specific for the lung tumor cell line LT391-06 were generated. Total mRNA from 2 x 10<sup>6</sup> cells from 15 such clones was isolated using Trizol reagent and cDNA was synthesized using Ready-to-Go kits (Pharmacia). To determine Va and Vb sequences in these clones, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb13 subfamily. Using cDNA generated from one of the clones (referred to as 1105), the Va sequence expressed was determined to be Va22. To clone the full TCR alpha and beta chains from clone 1105, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. Standard 35-cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the primers, with PWO (BMB) as the

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thermostable polymerase. The resultant specific bands (approximately 850 bp for the alpha chain and approximately 950 bp for the beta chain) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing the full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were sequenced. The determined cDNA sequences for the alpha and beta chains are provided in SEQ ID NO: 583 and 582, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO: 584 and 585, respectively.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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#### **CLAIMS**

## What is Claimed:

- 1. An isolated polynucleotide comprising a sequence selected from the group consisting of:
- (a) sequences provided in SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583;
- (b) complements of the sequences provided in SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583;
- (d) sequences that hybridize to a sequence provided in SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583, under moderately stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583;
- (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583; and
- (g) degenerate variants of a sequence provided in SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583.
- 2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
  - (a) SEQ ID NO: 584-587;
  - (b) sequences encoded by a polynucleotide of claim 1; and
- (c) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (d) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

- 3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.
- 4. A host cell transformed or transfected with an expression vector according to claim 3.
- 5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.
- 6. A method for detecting the presence of a cancer in a patient, comprising the steps of:
  - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.
- 7. A fusion protein comprising at least one polypeptide according to claim 2.
- 8. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 390, 392, 394, 396, 398-420, 422-424, 428-433 and 440-583 under moderately stringent conditions.
- 9. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
  - (a) polypeptides according to claim 2;

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- (b) polynucleotides according to claim 1; and
- (c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 10. An isolated T cell population, comprising T cells prepared according to the method of claim 9.
- 11. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:
  - (a) polypeptides according to claim 2;
  - (b) polynucleotides according to claim 1;
  - (c) antibodies according to claim 5;
  - (d) fusion proteins according to claim 7;
  - (e) T cell populations according to claim 10; and
- (f) antigen presenting cells that express a polypeptide according to claim 2.
- 12. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 11.
- 13. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 11.
- 14. A method for determining the presence of a cancer in a patient, comprising the steps of:
  - (a) obtaining a biological sample from the patient;

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- (b) contacting the biological sample with an oligonucleotide according to claim 8;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.
- 15. A diagnostic kit comprising at least one oligonucleotide according to claim 8:
- 16. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.
- 17. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate;
- (b) administering to the patient an effective amount of the proliferated T cells,

and thereby inhibiting the development of a cancer in the patient.

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#### SEQUENCE LISTING

<110> Corixa Corporation
 Reed, Steven G.
 Henderson, Robert A.
 Lodes, Michael J.
 Fling, Steven P.
 Mohamath, Raodoh
 Algate, Paul A.
 Secrist, Heather
 Indirias, Carol Yoseph
 Benson, Darin R.
 Elliot, Mark
 Mannion, Jane
 Kalos, Michael D.

<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

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Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
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Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
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Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Asp Asp Leu
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
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Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
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Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
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Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
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Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
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Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
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Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
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                                   250
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
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 Thr
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	_		Leu 100	_	_			105					110	_	-	
	-	115	Lys				120			_		125	-			
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	_		Glu	85		_			90			_		95		
			Lys 100				_	105					110			
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265

260

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Val Asn Gln Glu Asn Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala 55

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Arg Val Pro Glu Asn Thr Met His Ala Met Gln Gln Lys Leu Glu Asp

Phe Arg Asp Tyr Arg Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys 105

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<213> Homo sapien

<400> 74

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<213> Homo sapien

<400> 75

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Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln 55

Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro

Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser 90 Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu

100 105

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Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser
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<210> 79 <211> 2790 <212> DNA

<213> Homo sapien

<400> 79

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<210> 80 <211> 1460 <212> DNA <213> Homo sapien

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<210> 81 <211> 386

<212> PRT

## <213> Homo sapien

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<210> 82

<211> 418

<212> PRT

<213> Homo sapien

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<211> 418 <212> PRT <213> Homo sapien

<400> 83

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55 60 Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His 70 Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp 85 90 Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu 105 Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn 120 Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val 140 135 Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu

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Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
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Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
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Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
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Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
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Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
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Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
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Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
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Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
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His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
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His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
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Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
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Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
          100
                              105
                                                  110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
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Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
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Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn

185

Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val

170

Phe	Glu	Ser	Ile	Pro	Val	Pro	Lys	Asn	Ala	Lys	Glu	Lvs	Glu	Val	Pro
			20					25					30		
Leu	Glu	Glu 35	Glu	Met	Leu	Ile	Gln 40	Ser	Glu	Lys	Lys	Thr 45	Gln	Leu	Ser
Lys	Thr 50	Glu	Ser	Val	Lys	Glu 55	Ser	Glu	Ser	Leu	Met 60	Glu	Phe	Ala	Gln
Pro 65	Glu	Ile	Gln	Pro	Gln 70	Glu	Phe	Leu	Asn	Arg 75	Arg	Туг	Met	Thr	Glu 80
Val	Asp	Туг	Ser	Asn 85	Lys	Gln	Gly	Glu	Glu 90	Gln	Pro	Trp	Glu	Ala 95	Asp
Tyr	Ala	Arg	Lys 100	Pro	Asn	Leu	Pro	Lys 105	Arg	Trp	Asp	Met	Leu 110	Thr	Glu
Pro	Asp	Gly 115	Gln	Glu	Lys	Lys	Gln 120	Glu	Ser	Phe	Lys	Ser 125	Trp	Glu	Ala
Ser	Gly 130	Lys	His	Gln	Glu	Val 135	Ser	Lys	Pro	Ala	Val 140	Ser	Leu	Glu	Gln
Arg 145	Lys	Gln	Asp	Thr	Ser 150	Lys	Leu	Arg	Ser	Thr 155	Leu	Pro	Glu	Glu	Gln 160
Lys	Lys	Gln	Glu	Ile 165	Ser	Lys	Ser	Lys	Pro 170	Ser	Pro	Ser	Gln	Trp 175	_
			180	_				185	_				190	Gln	-
Lys	Gln	Glu 195	Thr	Pro	Lys	Leu	Trp 200	Pro	Val	Gln	Leu	Gln 205	Lys	Glu	Gln
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Glu 225	Gln	Asn	Thr	Thr	Lys 230	Ser	Trp	Thr	Thr	Pro 235	Met	Cys	Glu	Glu	Gln 240
Asp	Ser	Lys	Gln	Pro 245	Glu	Thr	Pro	Lys	Ser 250	Trp	Glu	Asn	Asn	Val 255	Glu
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Trp	Gly	Val 275	Ala	Thr	Ala	Ser	Leu 280	Ile	Pro	Asn	Asp	Gln 285	Leu	Leu	Pro
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305					310					315				Arg	320
				325					330					Asn 335	
			340					345					350	Ile	
		355					360					365		Ser	_
	370		•			375			•		380			Leu	
385					390					395				Glu	400
				405			_	_	410					Thr 415	
			420					425					430	Val	
Gln		435					440					445	1	Asp	
Thr	450					455					460			Gln	
Asn 465	Val	Phe	Pro	Arg	Pro 470	Thr	Gln	Pro	Phe	Val 475	Asn	Ser	Arg	Gly	Ser 480

Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg

Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser

WO 01/72295 PCT/US01/09991

490

505 Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr 520 Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys 535 Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp 550 555 Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe 565 570 Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val 580 585 Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val 600 Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr 615 Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu 630 635 Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe 645 650 Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys 660 665 Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu 680 Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr 695 Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp 710 715 Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser 725 Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp 740 <210> 186 <211> 705 <212> PRT <213> Homo sapien <400> 186 Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu 10 Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr 25 Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys 40 Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr 55 60 Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu 75 Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys 1 85 Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val 105 Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg

Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys

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145					150					155					160
Glu	Met	Gly	His	Ala 165	Glu	Thr	Tyr	Ala	Glu 170	Туг	Met	Pro	Ile	Lys 175	Leu
Lys	Ile	Gly	Leu 180	Arg	His	Pro	Asp	Ala 185	Val	Val	Glu	Thr	Ser 190	Ser	Leu
Ser	Ser	Val 195	Thr	Pro	Pro	Asp	Val 200	Trp	Tyr	Lys	Thr	Ser 205	Ile	Ser	Glu
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Thr 225	Tyr	Ala	Ala	Gln	Gln 230	His	Glu	Thr	Phe	Leu 235	Pro	Asn	Gly	Asp	Arg 240
Ala	Gly	Phe	Leu	Ile 245	Gly	Asp	Gly	Ala	Gly 250		Gly	Lys	Gly	Arg 255	Thr
Ile	Ala	Gly	Ile 260	Ile	Tyr	Glu	Asn	Tyr 265	Leu	Leu	Ser	Arg	Lys 270	Arg	Ala
Leu	Trp	Phe 275	Ser	Val	Ser	Asn	Asp 280	Leu	Lys	Tyr	Asp	Ala 285	Glu	Arg	Asp
Leu	Arg 290	Asp	Ile	Gly	Ala	Lys 295	Asn	Ile	Leu	Val	His 300	Ser	Leu	Asn	Lys
Phe 305			Gly		Ile 310	Ser	Ser	Lys	His	Asn 315	Gly	Ser	Val	Lys	Lys 320
Gly	Val	Ile	Phe	Ala 325	Thr	Tyr	Ser	Ser	Leu 330	Ile	Gly	Glu	Ser	Gln 335	Ser
Gly	Gly	Lys	Tyr 340	Lys	Thr	Arg	Leu	Lys 345	Gln	Leu	Leu	His	Trp 350	Cys	Gly
Asp	Asp	Phe 355	Asp	Gly	Val	Ile	Val 360	Phe	Asp	Glu	Cys	His 365	Lys	Ala	Lys
Asn	Leu 370	Суѕ	Pro	Val	Gly	Ser 375	Ser	Lys	Pro	Thr	Lys 380	Thr	Gly	Leu	Ala
Val 385	Leu	Glu	Leu	Gln	Asn 390	Lys	Leu	Pro	Lys	Ala 395	Arg	Val	Val	Tyr	Ala 400
Ser	Ala	Thr	Gly	Ala 405	Ser	Glu	Pro	Arg	Asn 410	Met	Ala	Tyr	Met	Asn 415	Arg
Leu	Gly	Ile	Trp 420	Gly	Glu	Gly	Thr	Pro 425	Phe	Arg	Gļu	Phe	Ser 430	Asp	Phe
Ile			Val		_	_	_		-					Val	Ala
Met	Asp 450	Met	Lys	Leu	Arg	Gly 455	Met	Tyr	Ile	Ala	Arg 460	Gln	Leu	Ser	Phe
Thr 465	Gly	Val	Thr	Phe	Lys 470	Ile	Glu	Glu	Val	Leu 475	Leu	Ser	Gln	Ser	Tyr 480
Val	Lys	Met	Tyr	Asn 485	Lys	Ala	Val	Lys	Leu 490	Trp	Val	Ile	Ala	Arg 495	Glu
Arg	Phe	Gln	Gln 500	Ala	Ala	Asp	Leu	Ile 505	Asp	Ala	Glu	Gln	Arg 510	Met	Lys
Lys	Ser	Met 515	Trp	Gly	Gln	Phe	Trp 520	Ser	Ala	His	Gln	Arg 525	Phe	Phe	Lys
Tyr	Leu 530	Cys	Ile	Ala	Ser	Lys 535	Val	Lys	Arg	Val	Val 540	Gln	Leu	Ala	Arg
Glu 545	Glu	Ile	Lys	Asn	Gly 550	Lys	Суѕ	Val	Val	Ile 555	Gly	Leu	Gln	Ser	Thr 560
Gly	Glu	Ala	Arg	Thr 565	Leu	Glu	Ala	Leu	Glu 570	Glu	Gly	Gly	Gly	Glu 575	Leu
Asn	Asp	Phe	Val 580	Ser	Thr	Ala	Lys	Gly 585	Val	Leu	Gln	Ser	Leu 590	Ile	Glu
Lys	His	Phe	Pro	Ala	Pro	Asp	Arg	Lys	Lys	Leu	Tyr	Ser	Leu	Leu	Gly

600 Ile Asp Leu Thr Ala Pro Ser Asn Asn Ser Ser Pro Arg Asp Ser Pro 615 Cys Lys Glu Asn Lys Ile Lys Lys Arg Lys Gly Glu Glu Ile Thr Arg 630 635 Glu Ala Lys Lys Ala Arg Lys Val Gly Gly Leu Thr Gly Ser Ser Ser 650 Asp Asp Ser Gly Ser Glu Ser Asp Ala Ser Asp Asn Glu Glu Ser Asp 660 665 Tyr Glu Ser Ser Lys Asn Met Ser Ser Gly Asp Asp Asp Phe Asn 680 Pro Phe Leu Asp Glu Ser Asn Glu Asp Asp Glu Asn Asp Pro Trp Leu 695 Ile 705 <210> 187 <211> 595 <212> PRT <213> Homo sapien <400> 187 Glu Ser Pro Arg His Arg Gly Glu Gly Gly Glu Trp Gly Pro Gly Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr 25 Pro Lys Glu Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro 40 Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu 70 75 His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu 90 Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala 105 Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly 120 125 Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser 135 Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg 150 155 Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg 165 170 Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg 185 Pro Arg Lys Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu 200 Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala 215 220 Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Pro 230 235 Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly 245 250 Thr Gln Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg 265 270 Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg 275 280

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100

WO 01/72295 PCT/US01/09991 82

90

Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys

105

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Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser 120 Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His 135 140 Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly 150 <210> 190 <211> 146 <212> PRT <213> Homo sapien <400> 190 Met Asp Pro Arg Ala Ser Leu Leu Leu Gly Asn Val Tyr Ile His Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser 20 25 Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser 40 Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His 55 Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu 70 75 Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp 85 90 Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile 105 Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser 120 Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile 135 Ile Leu 145 <210> 191 <211> 704 <212> PRT <213> Homo sapien <400> 191 Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu 10 Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe 25 Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser 40 Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr 55 Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala 70 75 Leu Arg Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu 105 Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu 120 125 Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe 135 140

145			Met		150	_		_		155		-		_	160
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Leu	Ala 210	Leu	Met	Gln	Lys	Lys 215	Leu	Ala	Asp	Tyr	Leu 220	Lys	Val	Leu	Ile
Asp 225	Asn	Lys	His	Leu	Leu 230	Ser	Glu	Phe	Tyr	Glu 235	Pro	Glu	Ala	Leu	Met 240
Met	Glu	Glu	Glu	Gly 245	Met	Val	Ile	Val	Gly 250	Leu	Leu	Val	Gly	Leu 255	Asn
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Val	Gly	Val 275	Ile	Asp	Phe	Ser	Leu 280	Tyr	Leu	Lys	Asp	Val 285	Gln	Asp	Leu
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Asn 305	Tyr	Val	Glu	Glu	Leu 310	Asn	Arg	His	Leu	Ser 315	Cys	Thr	Val	Gly	Asp 320
Leu	Gln	Thr	Lys	Ile 325	Asp	Gly	Leu	Glu	Lys 330	Thr	Asn	Ser	Lys	Leu 335	Gln
Glu	Glu	Leu	Ser 340	Ala	Ala	Thr	Asp	Arg 345	Ile	Cys	Ser	Leu	Gln 350	Glu	Glu
Gln	Gln	Gln 355	Leu	Arg	Glu	Gln	Asn 360	Glu	Leu	Ile	Arg	Glu 365	Arg	Ser	Glu
	370		Glu			375		_		-	380				
Tyr 385	Lys	Gln	Thr	Arg	Gln 390	Gly	Leu	Asp	Glu	Met 395	Tyr	Ser	Asp	Val	Trp 400
Lys	Gln	Leu	Lys	Glu 405	Glu	Lys	Lys	Val	Arg 410	Leu	Glu	Leu	Glu	Lys 415	Glu
Leu	Glu	Leu	Gln 420	Ile	Gly	Met	Lys	Thr 425	Glu	Met	Glu	Ile	Ala 430	Met	Lys
Leu	Leu	Glu 435	Lys	Asp	Thr	His	Glu 440	Lys	Gln	Asp	Thr	Leu 445	Val	Ala	Leu
Arg	Gln 450	Gln	Leu	Glu	Glu	Val 455	Lys	Ala	Ile	Asn	Leu 460	Gln	Met	Phe	His
Lys 465	Ala	Gln	Asn	Ala	Glu 470	Ser	Ser	Leu	Gln	Gln 475	Lys	Asn	Glu	Ala	Ile 480
Thr	Ser	Phe	Glu	Gly 485	Lys	Thr	Asn	Gln	Val 490	Met	Ser	Ser	Met	Lys 495	Gln
Met	Glu	Glu	Arg 500	Leu	Gln	His	Ser	Glu 505	Arg	Ala	Arg	Gln	Gly 510	Ala	Glu
Glu	Arg	Ser 515	His	Lys	Leu	Gln	Gln 520	Glu	Leu	Gly	Gly	Arg 525	Ile	Gly	Ala
Leu	Gln 530	Leu	Gln	Leu	Ser	Gln 535	Leu	His	Glu	Gln	Cys 540	Ser	Ser	Leu	Glu
Lys 545	Glu	Leu	Lys	Ser	Glu 550	Lys	Glu	Gln	Arg	Gln 555	Ala	Leu	Gln	Arg	Glu 560
Leu	Gln	His	Glu	Lys 565	Asp	Thr	Ser	Ser	Leu 570	Leu	Arg	Met	Glu	Leu 575	Gln
Gln	Val	Glu	Gly 580	Leu	Lys	Lys	Glu	Leu 585	Arg	Glu	Leu	Gln	Asp 590	Glu	Lys
Ala	Glu	Leu 595	Gln	Lys	Ile	Cys	Glu 600	Glu	Gln	Glu	Gln	Ala 605	Leu	Gln	Glu

Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys 615 Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu 630 635 Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg 645 650 Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser 665 Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys 680 Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser 695 <210> 192 <211> 331

<212> PRT

<213> Homo sapien

<400> 192

Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser 10 Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val 25 Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu 40 His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp 55 60 Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe 85 Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp 100 105 Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp 120 Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val 135 140 Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser 150 155 Leu Glu Val Ser Leu Gly Glu Leu Glu Leu Leu Ala Gln Glu Ala 165 170 Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu 185 Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu 200 Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu 215 220 Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala 230 235 Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser 245 250 Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys 265 260 270 Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys 280 Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg 295 Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln

310 320 Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu 325 <210> 193 <211> 475 <212> PRT <213> Homo sapien <400> 193 Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu 10 Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser 25 Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp 55 Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Gly Asp Thr Ser Leu Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His 85 90 Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln 105 Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg 120 Pro Val Val Ser Pro Ala Asn Gly Val Gly Val Arg Val Asp Gln 135 Asp Asp Asp Gln Asp Ser Ser Ser Leu Lys Leu Ser Gln Asn Ile Ala 150 155 Val Gln Thr Asp Phe Lys Thr Ala Asp Ser Glu Val Asn Thr Asp Gln 170 165 Asp Ile Glu Lys Asn Leu Asp Lys Met Met Thr Glu Arg Thr Leu Leu 185 190 Lys Glu Arg Tyr Gln Glu Val Leu Asp Lys Gln Arg Gln Val Glu Asn 200 Gln Leu Gln Val Gln Leu Lys Gln Leu Gln Gln Arg Arg Glu Glu Glu 215 220 Met Lys Asn His Gln Glu Ile Leu Lys Ala Ile Gln Asp Val Thr Ile 230 235 Lys Arg Glu Glu Thr Lys Lys Ile Glu Lys Glu Lys Glu Phe 245 Leu Gln Lys Glu Gln Asp Leu Lys Ala Glu Ile Glu Lys Leu Cys Glu 265 Lys Gly Arg Arg Glu Val Trp Glu Met Glu Leu Asp Arg Leu Lys Asn 280 Gln Asp Gly Glu Ile Asn Arg Asn Ile Met Glu Glu Thr Glu Arg Ala 295 300 Trp Lys Ala Glu Ile Leu Ser Leu Glu Ser Arg Lys Glu Leu Leu Val 310 315 Leu Lys Leu Glu Glu Ala Glu Lys Glu Ala Glu Leu His Leu Thr Tyr 325 330 Leu Lys Ser Thr Pro Pro Thr Leu Glu Thr Val Arg Ser Lys Gln Glu 340 345 Trp Glu Thr Arg Leu Asn Gly Val Arg Ile Met Lys Lys Asn Val Arg 360 · 365 Asp Gln Phe Asn Ser His Ile Gln Leu Val Arg Asn Gly Ala Lys Leu 375

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Ser Ser Leu Pro Gln Ile Pro Thr Pro Thr Leu Pro Pro Pro Ser
     390
                       395 400
Glu Thr Asp Phe Met Leu Gln Val Phe Gln Pro Ser Pro Ser Leu Ala
              405
                                410
Pro Arg Met Pro Phe Ser Ile Gly Gln Val Thr Met Pro Met Val Met
                            425
Pro Ser Ala Asp Pro Arg Ser Leu Ser Phe Pro Ile Leu Asn Pro Ala
                        440
Leu Ser Gln Pro Ser Gln Pro Ser Ser Pro Leu Pro Gly Ser His Gly
                    455
Arg Asn Ser Pro Gly Leu Gly Ser Leu Val Ser
                 470
     <210> 194
     <211> 241
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<213> Homo sapien

<400> 194

Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys 25 Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg 40 His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe 55 Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly 70 Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala 90 Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys 105 100 Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly 120 Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Ala Gly Leu Lys Glu 135 140 Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys 150 155 Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu 165 170 Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys 185 Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu 200 Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly 210 215 220 Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly 230 235 Leu

<210> 195

<211> 138

<212> PRT

<213> Homo sapien

<400> 195

Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu 25 Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu 40 Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys 55 Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu 70 75 Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln 120 Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln 135 <210> 196 <211> 102 <212> PRT <213> Homo sapien <400> 196 Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr 10 Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala 25 Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys 40 Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly Val Gly Thr Lys Ile Ala Glu; Lys Ile Asp Glu Phe Leu Ala Thr Gly 70 75 Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser Ile Asn Phe Leu Thr Arg 100 <210> 197 <211> 138 <212> PRT <213> Homo sapien <400> 197 Glu Ala Asn Glu Val Thr Asp Ser Ala Tyr Met Gly Ser Glu Ser Thr 10 Tyr Ser Glu Cys Glu Thr Phe Thr Asp Glu Asp Thr Ser Thr Leu Val His Pro Glu Leu Gln Pro Glu Gly Asp Ala Asp Ser Ala Gly Gly Ser Ala Val Pro Ser Glu Cys Leu Asp Ala Met Glu Glu Pro Asp His Gly Ala Leu Leu Leu Pro Gly Arg Pro His Pro His Gly Gln Ser Val 75 Ile Thr Val Ile Gly Gly Glu Glu His Phe Glu Asp Tyr Gly Glu Gly

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Ser Glu Ala Glu Leu Ser Pro Glu Thr Leu Cys Asn Gly Gln Leu Gly
                   105
Cys Ser Asp Pro Ala Phe Leu Thr Pro Ser Pro Thr Lys Arg Leu Ser
       115
                          120
                                              125
Ser Lys Lys Val Ala Arg Tyr Leu His Gln
                       1.35
      <210> 198
      <211> 100
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      <213> Homo sapien
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Met Thr Pro Ser Tyr Glu Ile Arg Ala Val Gly Asn Lys Asn Arg Gln
                                25
Lys Phe Met Cys Glu Val Gln Val Glu Gly Tyr Asn Tyr Thr Gly Met
                           40
Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp
                    55
Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val
                   70
                                       75
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
                                    90
Thr Thr Ala Asn
           100
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      <211> 127
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Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
Ala Thr Gln Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
                                25
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
                       55
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
                                       75
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
Arg Met Gln Arg Glu Arg Gly Lys Asn Val Val His Gln Leu Ser
                               105
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
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Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
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10 His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu 40 Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu 70 75 Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly 85

<210> 201

<211> 120

<212> PRT

<213> Homo sapien

<400> 201

Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala 10 Ser Ser Thr Pro Leu Ser Pro Thr Arg Ile Thr Arg Leu Gln Glu Lys 25 Glu Asp Leu Gln Glu Leu Asn Asp Arg Leu Ala Val Tyr Ile Asp Arg 40 Val Arg Ser Leu Glu Thr Glu Asn Ala Gly Leu Arg Leu Arg Ile Thr 55 Glu Ser Glu Glu Val Val Ser Arg Glu Val Ser Gly Ile Lys Ala Ala 70 Tyr Glu Ala Glu Leu Gly Asp Ala Arg Lys Thr Leu Asp Ser Val Ala 90 Lys Glu Arg Ala Arg Leu Gln Leu Glu Leu Ser Lys Val Arg Glu Glu 100 Phe Lys Glu Leu Lys Ala Arg Asn 115 120

<210> 202

<211> 177

<212> PRT

<213> Homo sapien

<400> 202

Met Ala Ala Gly Val Glu Ala Ala Glu Val Ala Ala Thr Glu Ile Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys 40 Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr 55 Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe 70 75 Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg 105 Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala 120 Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val

91

<210> 203 <211> 164 <212> PRT

<213> Homo sapien

<400> 203 Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu 25 His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val 40 Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr 55 Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr 70 75 Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu 90 Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr 105 Phe Tyr Tyr Ala Val Ala Val Lys Lys Asp Ser Gly Phe Gln Met 120 Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser 135 140 Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu 150

<210> 204 <211> 241 <212> PRT <213> Homo sapien

<400> 204

Pro Arg Lys Pro

 Met
 Ser
 Gly
 Gly
 Gly
 Gly
 Ser
 Ala
 Pro
 Pro
 Pro
 Fro
 Fro
 Fro
 Fro
 Fro
 Fro
 Fro
 Gly
 Ser
 Ile
 Arg
 Ile
 Tyr
 Ser
 Met
 Arg
 Phe
 Cys

 Pro
 Phe
 Ala
 Gly
 Arg
 Ile
 Arg
 Ile
 Ile

120 Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Asp Gly Leu Lys Glu 135 Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys 155 150 Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu 170 165 Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys 180 185 Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu 200 195 Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly 215 220 Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly 230 235 Leu <210> 205 <211> 160 <212> PRT <213> Homo sapien <400> 205 Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu 10 Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys 40 Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu 55 Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe 70 75 Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser 90 85 Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile 100 105 Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp 115 120 Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His 135 Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu 150 155 <210> 206 <211> 197 <212> PRT <213> Homo sapien <400> 206 Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser 25 Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro 40

Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly

55 Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His 70 Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu 105 Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu 120 Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu 135 Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro 150 155 Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met 165 170 Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu 180 185 His His Thr Glu Gly 195 <210> 207 <211> 175 <212> PRT <213> Homo sapien <400> 207 Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu 40 Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu 70 75 Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Glu Ala 8.5 90 Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu 105 Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His 120 . Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro 135 Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu 150 Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro 165 170 <210> 208 <211> 177 <212> PRT <213> Homo sapien <400> 208 Met Ala Ala Gly Val Glu Ala Ala Glu Val Ala Ala Thr Glu Ile 5 10 Lys Met Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly

25 Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr 55 Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe 75 Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly 90 Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg 105 Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala 115 120 Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val 135 140 Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val 150 155 Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Pro Gly Met 170 Ile

<210> 209 <211> 196 <212> PRT

<213> Homo sapien

<400> 209

Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp 25 Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile 40 Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr 55 Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu 70 75 Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln 85 90 Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val . 110 105 Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile 120 Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr 135 Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln 150 155 Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr 165 170 Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr 180 185 Thr Ile Ala Arg

<210> 210 <211> 156 <212> PRT

195

<213> Homo sapien

<400> 210 Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu 10 5 Val Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val Gly Tyr 40 Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser Gly Arg 55 Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val Thr Gln 70 75 Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp Leu Val 90 Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu Pro Lys 100 105 Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys Asp Ala 120 Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr Leu Trp 135 Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Lys 150 <210> 211 <211> 92 <212> PRT <213> Homo sapien <400> 211 Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln 10 Arg Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr 25 Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly 40 Lys Glu Val Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly 55 60 Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile 70 Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly <210> 212 <211> 142 <212> PRT <213> Homo sapien <400> 212 Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys 5 10 Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met 25 Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln

Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu

Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn

70 75 Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys 8.5 90 Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser 105 Glu Leu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val 120 Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly 135 <210> 213 <211> 142 <212> PRT <213> Homo sapien <400> 213 Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn Asp Arg 25 Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala Asn Gly 40 Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly 55 Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg 70 75 Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val Leu Gln 90 Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu 105 Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly Leu 120 Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu 135 <210> 214 <211> 129 <212> PRT <213> Homo sapien <400> 214 Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln Ile Thr 10 Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe Cys Leu 25 Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly Arg Pro 40 Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys 70 75 Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala Gly Ser 85 90 Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu Gly Lys 105

Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile 120

Glu

<210> 215 <211> 148 <212> PRT <213> Homo sapien <400> 215 Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu 10 Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val 20 25 Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu 40 Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala 70 75 Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Thr 90 Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln 105 Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr 120 115 125 Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu 135 Thr Tyr Val Thr 145 <210> 216 <211> 527 <212> PRT <213> Homo sapien <400> 216 Gln Arg Ala Pro Gly Ile Glu Glu Lys Ala Ala Glu Asn Gly Ala Leu 10 Gly Ser Pro Glu Arg Glu Glu Lys Val Leu Glu Asn Gly Glu Leu Thr 25 Pro Pro Arg Arg Glu Glu Lys Ala Leu Glu Asn Gly Glu Leu Arg Ser 40 Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly Gly Leu Thr Pro Pro Lys Ser Glu Asp Lys Val Ser Glu Asn Gly Gly Leu Arg Phe Pro Arg 70 75 Asn Thr Glu Arg Pro Pro Glu Thr Gly Pro Trp Arg Ala Pro Gly Pro 90 85 Trp Glu Lys Thr Pro Glu Ser Trp Gly Pro Ala Pro Thr Ile Gly Glu 105 100 110 Pro Ala Pro Glu Thr Ser Leu Glu Arq Ala Pro Ala Pro Ser Ala Val 115 120 Val Ser Ser Arg Asn Gly Gly Glu Thr Ala Pro Gly Pro Leu Gly Pro

135

150

165

Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro

Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu

Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly

155

170

			180					185					190		
Gly	Pro	Gly 195	Ser	Gly	Val	Asp	Ala 200	Lys	Ala	Gly	Trp	Val 205		Asn	Thr
Arg	Pro 210	Gln	Pro	Pro	Pro	Pro 215	Pro	Leu	Pro	Pro	Pro 220	Pro	Glu	Ala	Gln
Pro 225	Arg	Arg	Leu	Glu	Pro 230	Ala	Pro	Pro	Arg	Ala 235	Arg	Pro	Glu	Val	Ala 240
Pro	Glu	Gly	Glu	Pro 245	Gly	Ala	Pro	Asp	Ser 250	Arg	Ala	Gly	Gly	Asp 255	Thr
Ala	Leu	Ser	Gly 260	Asp	Gly	Asp	Pro	Pro 265	Lys	Pro	Glu	Arg	Lys 270	Gly	Pro
Glu	Met	Pro 275	Arg	Leu	Phe	Leu	Asp 280	Leu	Gly	Pro	Pro	Gln 285	Gly,	Asn	Ser
Glu	Gln 290	Ile	Lys	Ala	Arg	Leu 295	Ser	Arg	Leu	Ser	Leu 300	Ala	Leu	Pro	Pro
Leu 305	Thr	Leu	Thr	Pro	Phe 310	Pro	Gly	Pro	Gly	Pro 315	Arg	Arg	Pro	Pro	Trp 320
Glu	Gly	Ala	Asp	Ala 325	Gly	Ala	Ala	Gly	Gly 330	Glu	Ala	Gly	Gly	Ala 335	Gly
Ala	Pro	Gly	Pro 340	Ala	Glu	Glu	Asp	Gly 345	Glu	Asp	Glu	Asp	Glu 350	Asp	Glu
Glu	Glu	Asp 355	Glu	Glu	Ala	Ala	Ala 360	Pro	Gly	Ala	Ala	Ala 365	Gly	Pro	Arg
Gly	Pro 370	Gly	Arg	Ala	Arg	Ala 375	Ala	Pro	Val	Pro	Val 380	Val	Val	Ser	Ser
Ala 385	Asp	Ala	Asp	Ala	Ala 390	Arg	Pro	Leu	Arg	Gly 395	Leu	Leu	Lys	Ser	Pro 400
			Asp	405			_		410			-	_	415	-
			Phe 420					425					430		
		435	Asn				440					445	_	_	
	450		Thr			455					460			•	
465			Gly		470					475		_	_		480
	_		Glu	485					490			•		495	
Cys	Phe	Ser	Arg 500	Phe	Ser	Val	Ser	Pro 505	Ala	Leu	Glu	Thr	Pro 510	Gly	Pro
Pro	Ala	Arg 515	Ala	Pro	Asp	Ala	Arg 520	Pro	Ala	Gly	Pro	Val 525	Glu	Asn	
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<212> DNA

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tgcagattta tgccttattt tttagcattt tttaaatgtt gggtctttca aggtgttttt 900
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<212> DNA
<213> Homo sapiens
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<222> (538)
<223> n=A,T,C or G
<400> 261
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teteagagge caggaegace tgaaagagea getggeeatg gttgagegea gageeaacet 180
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agtggccgag caagagctac tggatgccag tgagcgcgtg cagctcctcc acacccagaa 300
caccaqcctc atcaacacca agaagaagct ggagacagac atttcccaaa tccagggaga 360
gatggaagac atcgtccagg aagcccgcaa cgcagaagag aaggccaaga aagccatcac 420
tgatgccgcc atgatggcgg aggagctgaa gaaggagcag gacaccagcg cccacctgga 480
geggatgaag aagaacatgg ageagaeeqt gaaggaeetg eageaeegte tggaegange 540
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<210> 262
<211> 594
<212> DNA
<213> Homo sapiens
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teggeageaa eeetgagaeg etttaeaget etagaeeeta aaaggteaaa aggeegtett 180
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geageeeegg attectecta ageegtgtee catetgtgeg ggaceeeact gaaaategga 540
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<213> Homo sapiens
<400> 263
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acttegacaa ataccaecea ggetaetttg ggaaagttgg tatgaageat taccaettaa 180
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tgcgatcggg ctactataaa gttctgggaa agggaaagct cccaaagcag cctgtcatcg 360
tgaaggccaa attetteage agaagagetg aggagaagat taagagtgtt gggggggeet 420
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aaaaaaaaa aaaaaaaaa ctcgag
                                                                   506
<210> 264
<211> 600
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (32)
<223> n=A,T,C or G
<400> 264
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cagtetttae taegeacaaa taaaagetge aageatgttg tgtggaaagg atetgetetg 480
gctgcgttgc actgtggaag accaectgag tcaccagtta actatggtag cccaeccage 540
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<211> 534
<212> DNA
<213> Homo sapiens
<400> 265
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aaagcccata tccacatgtt gctagagggg cttagagaac tacaaggcct gcagaatttc 480
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<210> 266
<211> 552
<212> DNA
<213> Homo sapiens
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attggatgct cacttagaga acctecttag caaagetgaa tgtaccaaaa tatggacaga 240
aaaaataatg aaacaaactg aagtgttatt gcagccaaat ccaaatgcca ggatagaaga 300
atttgtttat gagaaactgg atagaaaagc tccaagtcgt ataaacaacc cagaactttt 360
gggacaatat atgattgatg cagggactga gtttggccca ggaacagctt atggtaatgc 420
ccttattaaa tgtggagaaa cccaaaaaag aattggaaca gcagacagag aactgattca 480
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<211> 551
<212> DNA
<213> Homo sapiens
<400> 267
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catcaacaac agcatgeeec caggaegeac gggeatgggg acceegggga geeagatgge 180
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gecteceggg cagtggcage aggegeeeet teeceageag cageceatge caggettgee 300
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gcccagctcc cctcagcagc aacagcaggt gctgaacatt ctcaaatcaa acccgcagct 480
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gccccagcct g
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<211> 573
<212> DNA
<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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tgttcgtgat ccttgcatct gttacttagg gtcaaggctt gggtcttgcc ccgcagaccc 180
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<210> 271
<211> 447
<212> DNA
<213> Homo sapiens
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<210> 272
<211> 606
<212> DNA
<213> Homo sapiens
<400> 272
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aaactgaaga ccgaaactga caaagaaaat gctgaagtga agtttaaaga ttttcttctg 180
teettgaaga etatgatgtt ttetgaagat gaggetettt gtgttgtaga ettgetaaag 240
gagaagtetg gtgtaataca agatgettta aagaagteaa gtaagggaga attgaetaeg 300
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gctacaaagg atcggtgtaa gcagttaacc caggaaatga tgacagagaa agaaagaagc 420
aatgtggtta taacaaggat gaaagatcga attggaacat tagaaaagga acataatgta 480
tttcaaaaca aaatacatgt cagttatcaa gagactcaac agatgcagat gaagtttcag 540
caagttcgtg agcagatgga ggcagagata gctcacttga agcaggaaaa tgggtatact 600
ggaqaa
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<210> 273
<211> 598
<212> DNA
<213> Homo sapiens
<400> 273
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ctecaagece tteaggeege eccagtgtee testeettet eeggeeagae ecageeeege 180
gaagatggtg gaccgcgagc aactggtgca gaaagcccgg ctggccgagc aggcggagcg 240
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tgagatggtc cgtgcgtacc gggagaagat agagaaggag ttggaggctg tgtgccagga 480
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caaagtgttc tacctgaaga tgaaagggga ctactaccgc tacctggctg aagtggcc 598
<210> 274
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<212> DNA
<213> Homo sapiens
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gatggataat gctgactcaa gtcctgtggt agataagaga gaggttattg atttgcttaa 180
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aaaggacaag ttactcgctg ctgtgaagga agatgctgct gctacaaagg atcggtgtaa 480
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<210> 275
<211> 494
<212> DNA
<213> Homo sapiens
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<222> (379)
<223> n=A,T,C or G
<400> 275
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caccategag aatgteaagg caaagateca agataaggaa ggeatecete etgaeeagea 180
gaggetgate tttgetggaa aacagetgga agatgggege accetgtetg actacaacat 240
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gaagacactc actggcaaga ccatcaccct tgaggtggag cccagtgaca ccatcgagaa 360
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<210> 276
<211> 484
<212> DNA
<213> Homo sapiens
<400> 276
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<211> 513
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<213> Homo sapiens
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gagtgcggag aagcggaagg ccatgcttgg atgagctagc aatggaaacg ctgcaagaga 480
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<212> DNA
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<221> misc feature
<222> (457)
<223> n=A,T,C or G
<221> misc feature
<222> (471)
<223> n=A,T,C or G
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<212> DNA
<213> Homo sapiens
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<221> misc feature
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<223> n=A, T, C or G
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ggctggggga ggggcgcccg ccattgccca ngcttgctta ggtaaacaaa gcagccggga 480
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<212> DNA
<213> Homo sapiens
<220>
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<222> (456)
<223> n=A,T,C or G
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<211> 514
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (494)
\langle 223 \rangle n=A,T,C or G
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cattgagaca gaccgggggg tgcgagagca ggtgcgtttc tatgacaccc gggggctccg 300
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gcagcggcgt gtanacccaa atgtggctca acac
<210> 283
<211> 484
<212> DNA
<213> Homo sapiens
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tggaaacagc agaggacatc caggagaggc ggcagcaggt cctagaccga taccaccgct 180
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ttcaaagaga tgctgaagag ctggagaaat ggatacagga aaaacttcag attgcatctg 300
atgagaatta taaagaccca accaacttgc agggaaagct tcagaagcat caagcatttg 360
aagctgaagt gcaggccaac tcaggagcca ttgttaagct ggatgaaact ggaaacctga 420
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gccagtggga attacttttg gagaagatgc gaga
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<211> 383
<212> DNA
<213> Homo sapiens
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gcgagcggcc ggtgcagttc gagaaggcga accctgtcaa ctgcgtcttc ttcgatgagg 180
ccaacaagca ggtttttgct gttcgatctg gtggagctac tggcgtggta gttaaaggcc 240
cagatgatag gaatcccatc tcatttagaa tggatgacaa aggagaagtg aagtgcatta 300
agttttcctt agaaaataag atattggctg ttcagaggac ctcaaagact gtggattttt 360
gtaattttat ccctgataat tcc
<210> 286
<211> 943
<212> DNA
<213> Homo sapiens
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gttcaccggc ccgtctgccc cgaccgccca aggccgcctt cccctgacct cgcgcgcacg 180
cgtggggctg gggcggcgag gctggcggtc cggcctggcc gcgactctgc ccttctttcc 240
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teeggetgag cacegeeaac acetacteet accaeaaagt ggaettgeee tteeaggagt 360
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taggcggcgg tagggggtgg ggacgcttgg agtctccagg tgccaggatc cctgtccccg 480
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ttccacccca acaagaccac actggcctgg ctccgggaca catacccagc cctgccaccg 780
tetgeacgge ecetggagtg taccateegg getggtgagg tgetgtaett eecegaeege 840
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gaagatgaac aggagaggcc cttggccctc tgtgaaccag gtgtcaatcc cgaggaacaa 180
ctgattataa tccaaagtcg tctggatcag agtatggagg agaatcagga cttaaagaag 240
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cagagattga ctcagcagga cacatctgtt cttcagctca aacaagagct actgagggca 360
aatatggaca aagatgagct gcacaaccag aatgtggatc tgcagaggaa gctagatgag 420
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cagcaccagg ccaagttaga agaagcactc cggaaactct ctgatgtcag ttaccaccag 540
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gaggcagatg aggcgaccaa ctacaacagt cacaactctc aaagcaatgg ttttctcctt 660
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gttcgagatg ctctccgcag cctgcgcaac agcttcagtg gccacgatcc tcagcaccac 780
actattgaca gcttggagca gggcatttct agcctcatgg agcgcctgca tgttatggag 840
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gaataccggg agtcctggcc ccctaactca aagttgcctc actcacagag ctctccaact 960
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tgagttaatg ggccgggacc gaaacctagc cccggacgag aagcgcagca acgtgcggtg 180
ggaccacgag agcgtttgta aatattatct ctgtggtttt tgtcctgcgg aattgttcac 240
aaatacacgt tetgatettg gteegtgtga aaaaatteat gatgaaaate tacgaaaaca 300
gtatgagaag agetetegtt teatgaaagt tggetatgag agagattttt tgegataett 360
acagagetta ettgeagaag tagaaegtag gateagaega ggeeatgete gtttggeatt 420
atctcaaaac cagcagtctt ctggggccgc tggcccaaca ggcaaaaatg aagaaaaaat 480
tcaggttcta acagacaaaa ttgatgtact tctgcaacag attgaagaat tagggtctga 540
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1

```
aggaaaagta gaagaagccc aggggatgat gaaattagtt gagcaattaa aagaagagag 600
agaactgcta aggtccacaa cgtcgacaat tgaaaqcttt qctgcacaag aaaaacaaat 660
ggaagtttgt gaagtatgtg gagccttttt aatagtagga gatgcccagt cccgggtaga 720
tgaccatttg atgggaaaac aacacatggg ctatgccaaa attaaagcta ctgtagaaga 780
attaaaagaa aagttaagga aaagaaccga agaacctgat cgtgatgagc gtctaaaaaa 840
ggagaagcaa gaaagagaaa aaaaaaaaaa aaaaactcga g
<210> 289
<211> 987
<212> DNA
<213> Homo sapiens
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catttggact tgggctgggg caggggctgg tgttgggcaa agctgggggt ccaggctgga 180
gaagcagggg cccctccaga cgcagccttg ggagactcag catgtgcccc cctccctca 240
tcacagaaca agacaatggt taaaaaccag aacagatgcc cagaaggggg taccatggcc 300
attaccagca teteagacaa gggeaggett caaacaggga ggeetgtgge aacceetece 360
ctacgtctgg agctgagggg acagggggag ctgagaacaa agagaggaaa gaggagaaaa 420
geggeggggg aacaggeggg gagegtgate ttettqeece catetteete aggggttqqq 480
gggtacaaag tcggcggtgg cccatcccgc caggccccgc tgcccctcag aagaggccgc 540
agteetteag gttgttettg atgatgaeat eggtgaegge gteaaacaeg aactgeaegt 600
tettggtgte ggtggegeae gtgaagtgeg tgtagatete ettggtgtet ttgegettat 660
teaggteete aaacttaete tggatgtage tggetgeete ateatatttq ttggeecetq 720
tatactcagg gaagcagatg gtcaggggac tgtgtgtgat cttctcctca aacaggtcct 780
tettgttgag gaagaggatg atggaegtgt etgtgaacca ettgttgttg eagatgetat 840
egaatagett catgetetea tgcatgeggt teateteete gteeteaget ageaceaagt 900
cataggcgct caaggctacg cagaagatga tggctgtgac gccctcaaag cagtggatcc 960
acttetteeg etcagacege tgaceae
                                                                   987
       <210> 290
       <211> 300
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
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       \langle 223 \rangle n = A, T, C or G
       <400> 290
 gattcaaqat qtaccccatt qactttqaqa aqqatqatqa caqcaacttt catatqqatt
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 teategtgge tgeatecaae eteegggeag aaaaetatga eatteettet geagaeegge
                                                                        120
 acaagagcaa gctgattgca gggaagatca tcccagccat tgccacgacc acagcagccq
                                                                        180
 tggttggcct tgtgtgtctg gagctgtaca aggttgtgca ggggcaccga cancttgact
                                                                        240
 cetacangaa tgggtgcctc aacttgagcc ctgcctttct ttggtttctc tgaaccctt
                                                                        300
       <210> 291
       <211> 352
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(352)
       <223> n = A, T, C \text{ or } G
```

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cttctcaagg gtatttgcca tgtcccctga agagtttggc aagctggctc tgtggaagcg
                                                                       120
quatquete auguagaagg cetetetett etqutgqeee ceaectqete egqqaeqqee
                                                                       180
cccttacccc tgctgcttca gggtttttcc ccgqcgggtt gggaggggca ggaggtgggg
                                                                       240
tggaaatngg gtgggcncct ttcctcaggt agagnggggg gccaaaacct ctgcngtccc
                                                                       300
cggagngagc tatggacttt cttcccctc acaaggntgg gggcctcctg ct
                                                                       352
      <210> 292
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 292
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                                                                        60
ctatgccagg cgcatctcag ctaatccaaa agtaaatgag aaacttagaa aaagattgcc
                                                                       120
aattccaaat caacatattt agagaaaatt ggaaaaggag aagcttacta cagctttatt
                                                                       180
tgaggacttt ttaaagaacg ctgggttcta tctgtgagct gcaaatcttg gagcaaaaac
                                                                       240
cagagacatt gccagagcaa acaagaacag aaatacaaat ggagaactgg tcaaaagaca
                                                                       300
taacccacag ttatcttgaa caagaaacta cggggataaa taaaagtacg canccagatg
                                                                       360
agcaactgac tatgaattct gagaaaagta tgcatcggaa atccactgaa ttagntaatg
                                                                       420
aaataacatg ngagaacaca gaatggccag gggcagagat caacgaattt tcanatcatc
                                                                       480
agttcttatc cagatgatga gtctgtttac t
                                                                       511
      <210> 293
      <211> 526
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(526)
      <223> n = A, T, C or G
      <400> 293
gataaaaaga actttaatgg aaggcactgt tgtccaaaat cacataaagg gtaagagccc
                                                                        60
acacggtace accetgetet cetacttete aaacceacat ceaccaceca gacaggaggg
                                                                       120
tgcanacccc acaggaaatt acctcccgga gcactgactg atatttttcc ttaaaacaaa
                                                                       180
aaaatggctg tctcagacta ataacagaac atcttaagag ctataccagc tattacagcc
                                                                       240
tggtaatana agcagctttc taanaattcc caagtttata anaggcccaa naaatgcatt
                                                                       300
tattctgttg tctattaagc ctccatgaca aggagaaagt tatgagtaaa tccttggttc
                                                                       360
atcaggagtt aagagctgtg ngcctcatga ggagttaana gctgtgtgca taagcaggtt
                                                                       420
caagaaacaa actootgttt gtttgcctct ttgatggttc aaaaacattc agotgctttc
                                                                       480
acctctanga caaaatgctt aaagaattta ctctcatcac cttggg
                                                                       526
      <210> 294
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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<222> (1)...(601)
      <223> n = A, T, C or G
      <400> 294
actttaaaag ccaaatatat ttttaaaaga tcatgcttat aataagtaaa ttacncatta
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aggaaacatc aaaataaagt agatgaataa aaaggcacac tcgaaaaatt tgagcgcaga
                                                                       120
aaggacagtt ctttttgttt tgtttctaat gtcggaagaa aaagaaagag atatattaaa
                                                                       180
atcattgttt tcaagtgaag gtttctgtca gttgaagtag ttagcaatgg cttcttttct
                                                                       240
cccgtgtcca aagcaggctc ttcctgcgct gacttctgag gaggngttca gtcctctgcc
                                                                       300
atgtataggc gatacatcaa ggcgacggcc actgcagaga tggcagggat cacccagttg
                                                                       360
gtccaccaac tggaactaga atcaatagta gtgataagag tttccggagg cttgtttaac
                                                                       420
tttggtctgt catctggatg gagctcccca atgatgaatg ttttggacat ttccctggca
                                                                       480
tetgtagant gecegaeate etcaaagtte teagtageng teaceteeae ttgtteeett
                                                                       540
aaaacttctt ccccaccagg atgetettee agaaatttgg gneaaategn acacettgtg
                                                                       600
                                                                       601
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      <211> 262
      <212> DNA
      <213> Homo sapien
      <400> 295
cccttagccc caagggccct gggggcagcc accctcccgc ctgtcggccc gtagatttat
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caagggtgtt atgggcccag ctttgggggg ccagtcccga tgcactttga ggggtgttgg
                                                                       120
agaggggact cccccactcg cacttaactc aacggctctc gggccctggg gctqttttta
                                                                       180
ccatgtttgt ttttgaagct caggtgtctc acgtctgggc tgcaccaggc gaagagagaa
                                                                       240
attaaagatt tgaggttttt cc
                                                                       262
      <210> 296
      <211> 598
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(598)
      <223> n = A, T, C or G
      <400> 296
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                                                                        60
tacatcaaac aggccaaaaa aaataaacag caacttcata gacaaaaaag gaaaaaaaaa
                                                                       120
gaaacctttt atctttggcc tttttaacca tctcatacaa accaactact tatagtacag
                                                                       180
ctaagtacat acacaaaaaa gttactggaa tgctcggaat aagattgttt ttctgttgtc
                                                                       240
atttttgctt tttttacaag gntttttttc tcctttgaga ttataatgaa catggncaca
                                                                       300
ccacaagtaa agtcagaagt aggacagana acgctccgaa ggctggtttg gtcatccgan
                                                                       360
atcattaaaa atggctgacc ctaacaatat gtacaaaaat ataaaatgta aataaaaaat
                                                                       420
acaaacaaat ttccttttta aagtactttt aagaaaaaaa gcagggcctt ggaagttttg
                                                                       480
gttctttttt cctcccctqt tqcaaattct catqqtttqq gttqqqtqqn qqanancccq
                                                                       540
tgtcatctgc gggtggcact gccccggngg gcgggcgggc ctctctctcg aangngac
                                                                       598
      <210> 297
      <211> 509
      <212> DNA
      <213> Homo sapien
      <400> 297
                                                                        60
agaacacagg tgtcgtgaaa actaccccta aaagccaaaa tgggaaagga aaagactcat
                                                                       120
atcaacattg tcgtcattgg acacgtagat tcgggcaagt ccaccactac tggccatctg
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180 atctataaat geggtggeat egacaaaaga accattgaaa aatttgagaa ggaggetget gagatgggaa agggctcctt caagtatgcc tgggtcttgg ataaactgaa agctgagcgt 240 gaacgtggta tcaccattga tatctccttg tggaaatttg agaccagcaa gtactatgtg 300 actatcattg atgccccagg acacagagac tttatcaaaa acatgattac agggacatct 360 420 caggetgaet gtgetgteet gattgttget getggtgttg gtgaatttga agetggtate tocaagaatg ggcaggacco gagagcatgo cottotggot tacacactgg gtgtgaaaca 480 509 actaattgtc ggtgttaaca aaatggatt <210> 298 <211> 267 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(267) <223> n = A, T, C or G<400> 298 gggacggggg aaaggagacg cttcttcctc ttgctgctct tctcgttccc gagatcagcg 60 gcggcggtga ccgcgagtgg gtcggcaccg tctccggctc cgggngcnaa caatgctgac 120 tgatagcgga ggcggnggca cctccttnna ggaggacctg gactctgtgg ctccgcgatc 180 egeceeaget ggggeetegg ageegeetee geegggaggg gteggtetgg ggateeneae 240 267 cgngaggctn tttggggagg gcgggcc <210> 299 <211> 121 <212> DNA <213> Homo sapien <400> 299 ggcacgaggg ccctcggagc tcgtttccag atcgaggtaa gagggacttt cttaaaggcc 60 tagtctatgg gatggggcgg cggagggaat tttttgagaa ataaaatgaa gctgcagtgt 120 121 <210> 300 <211> 533 <212> DNA <213> Homo sapien <400> 300 aaggtgcaca gtatttgatg caggctgctg gtcttggtcg tatgaagcca aacacacttg 60 tccttggatt taagaaagát tggttgcaag cagatatgag ggatgtggat atgtatataa 120 acttatttca tgatgctttt gacatacaat atggagtagt ggttattcgc ctaaaagaag 180 gtctggatat atctcatctt caaggacaag aagaattatt gtcatcacaa gagaaatctc 240 ctggcaccaa ggatgtggta gtaagtgtgg aatatagtaa aaagtccgat ttagatactt 300 ccaaaccact cagtgaaaaa ccaattacac acaaagttga ggaagaggat ggcaagactg 360 caactcaacc actgttgaaa aaagaatcca aaggccctat tgtgccttta aatgtagctg 420 accaaaagct tcttgaagct agtacacagt ttcagaaaaa acaaggaaag aatactattg 480 533 atgtctggtg gctttttgat gatggaggtt tgaccttatt gataccttac ctt <210> 301 <211> 560 <212> DNA <213> Homo sapien <220> <221> misc\_feature

```
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      <223> n = A, T, C or G
      <400> 301
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                                                                        60
cctcggtcaa gatatagtca aataactatg gctgcaggtt ccacagttcc acaataacca
                                                                       120
tggctgcacg atccacaatt cagacacaga catagagctg gggtgggtgg aaggggcagg
                                                                       180
agggtggcag agtgcggact gtccccagcc ctggcctctc catgcanagt tggcccaggc
                                                                       240
agacacaccc catggaatga tqagaaagtg acggcacggc cccttcccac agcaagcctq
                                                                       300
gggctgccag gaactgccct tcanaacctt tgggcccagg tcnccctgaa nccccacaac
                                                                       360
tttttatctg gaataagtat taaaaaacaa taaattaagc aaacaacntg gnccttgaag
                                                                       420
gatgttgacc nacatggtcc acagtttttg gcncaaaaaa ataagggctg gtttgctttt
                                                                       480
tttggaagge agggtttgtg gnttggettt caaatnattt tcaaaccatt ccccagggag
                                                                       540
gganaacccc cgggggggaa
                                                                       560
      <210> 302
      <211> 599
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc feature
      <222> (1)...(599)
      <223> n = A, T, C or G
      <400> 302
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                                                                        60
tggaaagact tgtgcacaat agtttcccat ccgtactcag cctctcttgc cccgatcccc
                                                                       120
gacttttcta ctcaaggcca gggaaggcct ccaaggngat gggcggcagg taacgagtca
                                                                       180
ttgcctctca cgccacctgg aaggctggac tacttcctcc tcccaactgc ggggtcccan
                                                                       240
aaatcctcgg gtcccagngg ctgacttaca atattcaatt cactctgacc aaacttccta
                                                                       300
tganaaaatc cacggngagc caaaatgaaa agtacaaggc agtagtacag gaacctggca
                                                                       360
gccgcactgg ccgcccanaa acgtcagtgg ngctgcccca ttcggcgaaa ggttagggag
                                                                       420
caggaaaaga ggaagcagga gagggaagga aagtcccatg gaatatgtat tccanaatcc
                                                                       480
ttacattttc tcaqccaccq ctccccacqt qaqttcccac ccccaccccq acaaqaaqca
                                                                       540
aagagttetg aggateeaag aacgtgaeeg ggteanaean gtteagetae tgagtteae
                                                                       599
      <210> 303
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 303
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                                                                        60
cccgcgggcc gacgccgtac tggaggttgc gcctcggtgg cgccgcgctg ctcctgctgc
                                                                       120
teatceeggt ggeegeegeg eaggageete eeggagetge ttgtteteag aacacaaaca
                                                                       180
aaacctgtga agagtgcctg aagaacgtct cctgtctttg gtgcaacact aacaaggctt
                                                                       240
gtctggacta cccagttaca agcgtcttgc caccggcttc cctttgtaaa ttgagctctg
                                                                       300
cacgctgggg agtttgttgg gtgaactttg aggcgctgat catcaccatg tcggtagtcg
                                                                       360
ggggaaccct cctcctgggc attgccatct gctgctgctg ctgctgcagg aggaagagga
                                                                       420
gccggaagcc ggacaggagt gaggagaagg ccatgcgtga gcgggaggag aggcggatac
                                                                       480
                                                                       540
ggcaggagga acggagagca gagatgaaga caagacatga tgaaatcaga aaaaaatatg
                                                                       591
gcctgtttaa agaagaaaac ccgtatgcta gatttgaaaa caactaaagc g
      <210> 304
      <211> 441
      <212> DNA
      <213> Homo sapien
```

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<220>
      <221> misc feature
      <222> (1)...(441)
      <223> n = A, T, C or G
      <400> 304
gctggacgga gacctgctgg aggaggagga gctggaggaa gcagaggagg aggaccggtc
                                                                        60
gtcgctgctg ctgctgtcgc cgcccgcggc caccgcctct cagacccagc agatcccagg
                                                                       120
egggteeetg gggtetgtge tgetgeeage egeeaggtte gatgeeeggg aggeggegge
                                                                       180
ggcggcgggg gtgctgtacg gaggggacga tgcccagggc atgatggcgg cgatgctgtc
                                                                       240
ccacgcctac ggccccggcg gttgtggggc ggcggcggcc gccctgaacg gggagcaggc
                                                                       300
ggccctgctc cggagaaaga gcgtcaacac caccgagtgc gtcccggtgc ccagctccga
                                                                       360
gcacgtcgcc gagatcgtcg gccgccaggg ttgtaaaatt aaagcactga nagccaagac
                                                                       420
aaacacgtat atcaagactc c
                                                                       441
      <210> 305
      <211> 491
      <212> DNA
      <213> Homo sapien
      <400> 305
tegecatgee ecettettag eactgeaceg ceaggteeat getgetgeea eceeagaeet
                                                                        60
                                                                       120
gggctttgcc tgccacctct gtgggcagag cttccgaggc tgggttggccc tggttctgca
tetgegggee catteagetg caaageggee categettgt cecaaatgeg agagaegett
                                                                       180
ctggcgacga aagcagette gageteatet geggeggtge eacceteeeg eeeeggagge
                                                                       240
ccggcccttc atatgcggca actgtggccg gagctttgcc cagtgggacc agctagttgc
                                                                       300
ccacaagegg gtgcacgtag ctgaggeect ggaggaggee geagecaagg ctetggggee
                                                                       360
                                                                       420
ccggcccagg ggccgccccg cggtgaccgc cccccggccc ggtggagatg ccgtcgaccg
ccccttccag tgtgcctgtt gtggcaagcg cttccggcac aagcccaact tgatcgctca
                                                                       480
                                                                       491
cccgcgcgtg c
      <210> 306
      <211> 547
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(547)
      <223> n = A, T, C or G
      <400> 306
tctctttctt ttaagacagg aatgtaagcc acaacattta caaatacaat gttttaactc
                                                                        60
totacatgta ggaagecaac etgeteettt ttgatettet tetttggeac aaceteagtg
                                                                       120
gatttetetg atteagaacg agttetaatt gatettetet gttgettett ttetactgag
                                                                       180
cctgtagaac cagatgttgc ttcaggagat gatacactct gcgttggctt ttcatttctc
                                                                       240
tggtttggtg tagaaattat aagcetgtet tgeeecetga caettattte tgttttgtta
                                                                       300
ccaattccct ttgttgaata aacaaattga tcgataaatt tcccatcccc tgtagcattc
                                                                       360
                                                                       420
tgaagagcaa acacttgttc aattttcaca actggagaca tgttacactt ctgcaaatcc
aggeteeett tgtgeateeg taatggaage tggtaaggat tteettgetg eegeagtttt
                                                                       480
ecaggetatt ttaacaggeg gnggetette etettteege acttgtgtge egeetetgge
                                                                       540
tatgtct
                                                                       547
      <210> 307
      <211> 571
      <212> DNA
```

<213> Homo sapien

```
<220>
     <221> misc feature
     <222> (1)...(571)
     <223> n = A, T, C or G
     <400> 307
cgctgcatgt gataatgtca tcatttattt ttaaatggtt ctaaattgca natttaagtt
                                                                      60
gatttcaaat caaccctatt tttaaattac ttttaatagg aanaaatgaa gcaaggacat
                                                                     120
acataatcta ctatatttga aggactcaaa caaatacatg tttggctgtg aattctgtac
                                                                     180
tctcaccaaa acagagataa aaatccacct aaaatacact ttccttcatt tagtgcttgt
                                                                     240
ggganaaggt caagtattgc actttaaaat tactttcatc taacatttgc cccaactttc
                                                                     300
cccctgaatt cactatatgt tttcagcaaa catgatttta taaattttaa gtataaaagc
                                                                     360
420
aaacggcata tttacttaca aaattganag ataggggcat ccaqctgagg tacatttcct
                                                                     480
cccttggcgt tgagtttctg gacttgggtc gggggcacag gcttgtgtga ctgccccgtg
                                                                     540
gecegataca tggcetggae eccaggatge g
                                                                     571
     <210> 308
     <211> 591
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(591)
     <223> n = A, T, C or G
     <400> 308
ctccttatgt gtctgcctac ttcattcttc ggcatttcct gcttatccaa gttcaccatt
                                                                      60
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc
                                                                     120
aagttcacca tttcaggtca ccactggata tcagttgcct gtatataatt atcaggcatt
                                                                     180
tectgettat ecaagtteac cattteaggt caccactgga tateagttge etgtatataa
                                                                     240
ttatcaggca tttcctgctt atccaagttc accatttcag gtcaccactg gatatcagtt
                                                                     300
gcctgtatat aattatcagg catttcctgc ttatccaagt tcaccatttc aggtcaccac
                                                                     360
tggatatcag ttgcctgtat ataattatca ggcatttcct gcttatccaa gttcaccatt
                                                                     420
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc
                                                                     480
aaattcaqca qttcaqqtca ccactqqata tcaqttccat qtatacaatt accaqatqcc
                                                                     540
accgcagtgc cctgttgggg gagcaaagga gaaatntgtg gaccgaagca t
                                                                     591
     <210> 309
     <211> 591
     <212> DNA
     <213> Homo sapien
     <400> 309
agggggtgca cgtactccca actgtggtcg cgctctcacc ccttctgctg ctctcgtggc
                                                                      60
cccctcgcga tggcgggcat cctgtttgag gatattttcg atgtgaagga tattgacccg
                                                                     120
gagggcaaga agtttgaccg aggtaagtaa gtgtctcgac tgcattqtga qagtgaatct
                                                                    180
ttcaagatgg atctaatctt agatgtaaac attcaaattt accctqtaga cttqqqtqac
                                                                     240
aagtttcggt tggtcatagc tagtaccttg tatgaagatg gtaccctgga tgatggtgaa
                                                                     300
tacaacccca ctgatgatag gccttccagg gctgaccagt ttgagtatgt aatgtatgga
                                                                     360
aaagtgtaca ggattgaggg agatgaaact tctactgaag cagcaacacg cctgctgaga
                                                                     420
ttgagagetg ctgagtggca gtgctccaga atcacgggat ggggccttct gtttcagetc
                                                                     480
tgcgtacgtg tcctatgggg gcctgctcat gaggetgcag ggggatgcca acaacctgca
                                                                     540
tggattcgag gtggactcca gagtttatct cctgatgaag aagctagcct t
                                                                     591
```

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<211> 488
      <212> DNA
      <213> Homo sapien
      <400> 310
tggtctcaag cctgaagagg ctccgcccac aagctggccc atgaagttag caatgcctgt
                                                                        60
ggcttcagtc aattgtcttg agactgtgaa gaggctgaaa gacaccttcc cgggtggaag
                                                                       120
aaggagttca ctgaaaactt atcttaaact gacccttccc tttgagtgag tcttcattcc
                                                                       180
teteceatgt gggaacceag cetecgatge eeeggggaet aggggaaaca gttggaggte
                                                                       240
cgtgccgtcc ccagcctgcc acgggtgcga ggacagccaa gtcctgagtg actcaagatg
                                                                       300
cttcacttac atggaagaaa cttctaaaac tctaccgagt ggtttttgta tatactaaag
                                                                       360
ttctatttag agcttttctg ttttgggcaa gttcgctgct ccttctattt gggcactttg
                                                                       420
gtttttgtac tgtcttttgt gacggcattg attgaacatt ttttactagt agtcttatga
                                                                       480
cttttgta
                                                                       488
      <210> 311
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 311
cccgtttntg nagcaaaana gggggaagat ttataggtag aggcgacaaa cctaccgagc
                                                                        60
ctggtgatag ctggttgtcc aagatagaat cttagttcaa ctttaaattt gcccacagaa
                                                                       120
ccctctaaat ccccttgtaa atttaactgt tagtccaaag aggaacagct ctttggacac
                                                                       180
taggaaaaaa ccttgtagag agagtaaaaa atttaacacc catagtaggc ctaaaagcag
                                                                       240
ccaccaatta agaaagcgtt caagctcaac acccactacc taaaaaaatcc caaacatata
                                                                       300
actgaactcc tcacacccaa ttggaccaat ctatcaccct atagaagaac taatgttagt
                                                                       360
ataagtaaca tgaaaacatt ctcctccgca taagcctgcg tcagattaaa acactgaact
                                                                       420
gacaattaac agcccaatat ctacaatcaa ccaacaagte attattaccc tcactqtcaa
                                                                       480
cccaacacag gcatgctcat aaggaaaggt t
                                                                       511
      <210> 312
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 312
gaacttgcgt tgaaggaagc agaaactgat gaaataaaaa ttttgctgga agaaagcaga
                                                                        60
gcccagcaga aggagacctt gaaatctctt cttgaacaag agacagaaaa tttgagaaca
                                                                       120
gaaattagta aactcaacca aaagattcag gataataatg aaaattatca ggtgggctta
                                                                       180
gcagagctaa gaactttaat gacaattgaa aaaqatcagt qtatttccqa qttaattagt
                                                                       24.0
agacatgaag aagaatctaa tatacttaaa gctgaattaa acaaagtaac atctttgcat
                                                                       300
aaccaagcat ttgaaataga aaaaaaccta aaagaacaaa taattgaact gcagagtaaa
                                                                       360
ttggattcag aattgagtgc tcttgaaaga caaaaagatg aaaaaattac ccaacaagaa
                                                                       420
gagaaatacg aagctattat ccagaacctt qagaaaqaca qacaaaaatt qqtcaqcaqc
                                                                       480
caggagcaag acagagaaca gttaattcag aagcttaatt gtgaaaaaga tgaagctatt
                                                                       540
cagactgccc taaaagaatt taaattggag agagaagttg ttgagaaaga g
                                                                       591
      <210> 313
      <211> 373
      <212> DNA
      <213> Homo sapien
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<220>
      <221> misc feature
      <222> (1)...(373)
      <223> n = A, T, C or G
      <400> 313
ttgattttta ttctgnattt tattactgaa atangttgtc ctantnatcc caccccacaa
                                                                        60
taaaaatntn acceangeec ccentttett tneetnatne eetntteeac cacaccatee
                                                                       120
cggaacaagt gctccaggat tccctgccca ctggccattt tggagtgtgn ccattgggta
                                                                       180
gcaatgtgga aaccaccaag gcctttgtgg anaaaatgga gggggttgag ggagncccan
                                                                       240
gaggggctna tttgagggcc tttgccactt gctcataggc gagctcnatc tcctcntnat
                                                                       300
ctgnacangt ggaagcaaat tcttcccggg cgtnggnant gctnaagnac cgatgcactc
                                                                       360
cccggaaggn ctn
                                                                       373
      <210> 314
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(591)
      <223> n = A, T, C \text{ or } G
      <400> 314
cccgtgccgc cgccgcctcc tgggaagaga ggaagcggga gaggagccca cgtcgcctgt
                                                                        60
cacccaatat ctccagccgc gcagtcccga agagtgtaag atgttcgcct gcgccaagct
                                                                       120
cgcctgcacc ccctctctga tccgagctgg atccagagtt gcatacagac caatttctgc
                                                                       180
atcagtgtta tctcgaccag aggctagtag gactggagag ggctctacgg tatttaatgg
                                                                       240
ggcccagaat ggtgtgtctc agctaatcca aagggagttt cagaccagtg caatcagcag
                                                                       300
agacattgat actgctgcca aatttattgg tgcaggtgct gcaacagtag gagtggctgg
                                                                       360
ttctggtgct ggtattggaa cagtctttgg cagccttatc attggttatg ccagaaaccc
                                                                       420
ttcgctgaag cagcagctgt tctcatatgc tatcctggga tttgccttgt ctgaagctat
                                                                       480
gggtctcttt tgtttgatgg ttgctttctt gattttgttt gccatgtaac aaattactgc
                                                                       540
ttgacatgtt ggcattcata ttaattacng atgtaattct gtgtatctta c
                                                                       591
      <210> 315
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(591)
      <223> n = A, T, C or G
      <400> 315
aagcccttca ccaacaaaga tgcctatact tgtgcaaatt gcagtgcttt tgtccacaaa
                                                                        60
ggctgccgag aaagtctagc ctcctgtgca aaggtcaaaa tgaagcagcc caaagggagc
                                                                       120
cttcaggcac atgacacatc atcactgccc acggtcatta tgagaaacaa gccctcacag
                                                                       180
cccaaggage qtcctcggtc cgcaqtcctc ctgqtqqatg aaaccqctac caccccaata
                                                                       240
tttgccaata gacgatccca gcagagtgtc tcgctctcca aaagtgtctc catacagaac
                                                                       300
attactggag ttggcaatga tgagaacatg tcaaacacct ggaaattcct gtctcattca
                                                                       360
acagactcac taaataaaat cagcaaggtc aatgagtcaa cagaatcact tactgatgag
                                                                       420
ggtacagaca tgaatgaagg acaactactg ggagactttg agattgagtc caaacagctg 🕛
                                                                       480
gaagcagagt cttggagtcg gataatagac agcaagtttc taaaacagcc aaaagaaaga
                                                                       540
                                                                       591
tgtgggtcaa acngcgagaa gtaatatatg agttggatgc agacagagtt t
```

1.

```
<210> 316
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 316
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                                                                        60
gtaaatggaa aggagattat gaaaaactgg agcacaacca cacttacatt caatggcttt
                                                                       120
tccccctgag agaacaaggc ttgaacttct atgccaaaga actaactaca tatgaaattg
                                                                      180
aggaattcaa aaaaacaaaa gaagcaatta gaagattcct cctggcttat aaaatgatgc
                                                                      240
tagaattttt tggaataaaa ctgactgata aaactggaaa tgttgctcgg gctgttaact
                                                                      300
ggcaggaaag atttcagcat ctgaatgagt cccagcacaa ctatttaaga atcactcgta
                                                                       360
ttcttaaaag ccttggtgag cttggatatg aaagttttaa atctcctctt gtaaaattta
                                                                      420
ttcttcatga agctcttgtg gagaatacta ttcccaatat taagcagagt gctctagagt
                                                                      480
                                                                       540
attttgttta tacaattaga gacagaagag aaaggagaaa gctcctgcgg ttcgcccaga
aacactacac gccttcagag aactttatct ggggacccgc ctcgaaaaga a
                                                                      591
      <210> 317
      <211> 323
      <212> DNA
      <213> Homo sapien
      <400> 317
ccaagctacq gaagcaaqtq gaagagattt ttaatttgaa atttgctcaa gctcttggac
                                                                        60
tcaccgagge agtaaaagta ccatatcctg tgtttgaatc aaacccggag ttcttctatg
                                                                       120
tggaaggett gecagagggg attecettee gaageeetae etggtttgga attecaegae
                                                                      180
ttgaaaggat cgtccacggg agtaataaaa tcaagttcgt tgttaaaaaa cctgaactag
                                                                      240
ttatttccta cttgcctcct gggatggcta gtaaaataaa cactaaagct ttgcagtccc
                                                                      300
ccaaaagacc acgaagtcct ggg
                                                                      323
      <210> 318
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(591)
      <223> n = A, T, C or G
      <400> 318
gatggcgtac ttggcttgga gactggcgcg gcgttcgtgt ccgagttctc tgcaggtcac
                                                                        60
tagtttcccg gtagttcagc tgcacatgaa tagaacagca atgagagcca gtcagaagga
                                                                      120
ctttgaaaat tcaatgaatc aagtgaaact cttgaaaaag gatccaggaa acgaagtgaa
                                                                      180
gctaaaactc tacgcgctat ataagcaggc cactgaagga ccttgtaaca tgcccaaacc
                                                                       240
aggtgtattt gacttgatca acaaggccaa atgggacgca tggaatgccc ttggcagcct
                                                                       300
gcccaaggaa gctgccaggc agaactatgt ggatttggtg tccagtttga gtccttcatt
                                                                       360
ggaatcetct agtcaggtgg agectggaac agacaggaaa tcaactgggt ttgaaactet
                                                                       420
ggtggtgacc tccgaagatg gcatcacaaa gatcatgttc aaccggccca aaaagaaaaa
                                                                      480
tgccataaac actgagatgt atcatgaaat tatgcgtgca cttaaagctg ccagcaanga
                                                                      540
tgactcaatc atcacttgtt ttaacaggaa atggtgacta ttacagtagn g
                                                                      591
      <210> 319
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 319
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gaatteggea egaggttget getaagegaa egeeetttgg agettaegga ggeettetga
                                                                        60
aagaetteae tgetaetgae ttgtetgaat ttgetgeeaa ggetgeettg tetgetggea
                                                                       120
aagtctcacc tgaaacagtt gacagtgtga ttatgggcaa tgtcctgcag agttcttcag
                                                                       180
atgctatata tttggcaagg catgttggtt tgcgtgtggg aatcccaaag gagaccccag
                                                                       240
ctctcacgat taataggctc tgtggttctg gttttcagtc cattgtgaat ggatgtcagg
                                                                       300
aaatttgtgt taaagaagct gaagttgttt tatgtggagg aaccgaaagc atgagccaag
                                                                       360
ctccctactg tgtcagaaat gtgcgttttg gaaccaagct tggatcagat atcaagctgg
                                                                       420
                                                                       480
aagattettt atgggtatea ttaacagate agcatgteca getececatg geaatgaetg
cagagaatct tgctgtaaaa cacaaaataa gcagagaaga atgtgacaaa tatgccctgc
                                                                       540
agtcacagca gagatggaaa gctgctaatg atgctggcta ctttaatgat g
                                                                       591
      <210> 320
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(591)
      <223> n = A, T, C or G
      <400> 320
ggctccggcg tctgcagggg tcgccqagct aacccgtggc taggcgagtg gggcgggcg
                                                                        60
gccggcacca tgtcgaggca ggcgaaccgt ggcaccgaga gcaagaaaat gagctctgag
                                                                       120
ctcttcaccc tgacctatgg tgccctggtc acccagctat gtaaggacta tgaaaatgat
                                                                       180
gaagatgtga ataaacagct ggacaaaatg ggctttaaca ttggagtccg gctgattgaa
                                                                       240
gatttcttgg ctcggtcaaa tgttgggagg tgccatgact ttcgggaaac tgcggatgtc
                                                                       300
attgccaagg tggcgttcaa gatgtacttg ggcatcactc caagcattac taattggage *
                                                                       360
ccagctggtg atgaattctc cctcattttg gaaaataacc ccttggtgga ctttgtggaa
                                                                       420
cttcctgata accactcatc ccttatttat tccaatctct tgtgtggggt gttgcgggga
                                                                       480
gctttggaga tggtccagat ggctngngga ggcccaagtt tgtccaggac accctnaaag
                                                                       540
gagacgggng tgacagaaat ccggatgaga ttcatcaggc ggattganga c
                                                                       591
      <210> 321
      <211> 260
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(260)
      <223> n = A, T, C or G
      <400> 321
ctgcttggct ccacacgtgg gccgccgtag gtattccgac cggtaattcc tcctattggt
                                                                        60
                                                                       120
gtgcagcagc cacattgaag gatagagtgg cagcagaggc caaggatcgt gagttgatgg
agtttgctgc tgaaaatgaa gggaagtctg ggggaggtct ccacagcgta gctgaggggg
                                                                       180
                                                                       240
tgcggctaag tccagagcct ggcagggagg gagtaaggga cttagcaggg gcggaggagt
                                                                       260
tctgcggngg anaggagggg
      <210> 322
      <211> 559
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(559)
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<223> n = A, T, C or G<400> 322 ttccacatga catggagtgt gaagetggat gagcacatca ttccactggg aagcatggca 60 nttaacagca teteaaaact gactnanete acceagtett ceatgtatte actteetaat 120 gcacccactc tggcanacct gnaggacnat acacatgaag ncantgatga tcagccagan 180 aanceteact ttgacteteg canngtgata tttgagetgg atteatgeaa tggnagtggg 240 aaagtttgcc ttgtctacaa aagtgggaaa ccagnattag cagaanacac tgagatctgg 300 ttcctgnaca nancgttata ctggcatttt ctcacanaca cctttactgc ctattaccgc 360 ctgctcatca cccacctggg cctgccccag tggcaatatg ccttcccagc tatggcatta 420 gcccacaggc caagcaatgg ttcagcatgt ataaacctat cacctacaac acaaacctgc 480 tcacagaaga naccgactcc tttgtgaata agctagatcc canctnagtg tttaagagca 540 agaacaagat cgttatccc 559 <210> 323 <211> 492 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(492) <223> n = A, T, C or G<400> 323 cetgtetece ageegtacea gegagggete ggeeggeage geegggetgg ggggeggegg 60 120 cgccggcgcc ggagccgggg tgggtgcagg cggcggcggg ggcagcggcg cgagcagcgg eggeggggee ggggggetge aacceageag cegegetgge ggeggeegge ceteeageee 180 cagecegteg gtggtgageg agaaggagaa ggaagagttg gageggetge agaaagagga 240 300 ggaggagagg aagaagaggc tgcagctgta tgtgttcgtg atgcgctgca tcgcctaccc 360 ctttaatgcc aagcagccca ccgacatggc tcgccggcag cagaagatca gcaaacagca gctgcagaca gtcaaggace ggtttcaggc tttcctcaat ggggaaaccc anatcatggc 420 tgacgaagcc ttcatgaacc gctgtngcag agttactatg aggtgttcct gaagaccacc 480 cgtgtggccg ca 492 <210> 324 <211> 474 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (474) <223> n = A, T, C or G<400> 324 aatttcagca acatacttct caatttcttc aggatttaaa atcttgaggg attgatctcg 60 cctcatgaca gcaagttcaa tgtttttgcc acctgactga accacttcca ggagtgcctt 120 gatcaccage ttaatggtca natcatetgt tteaatgget tegteagtat agttettete 180 cagnaactca cgcactgact tggcaccccg gcctatggca ttggccttcc aggcatggta 240 tgtgcccgag gggtcagtct gatagagcct aggagtgcca tcaaagtcga aacccacgat 300 gagggcagag atgccaaacg gcctgcgccc attgctctgc gtataacgct gcttcanact 360 ggcgatgtag cgggtgatgt actccacagt gaccgggtcc tccacagtca gccggtggct 420 etggcactec accegggccc tgttgatgac tatcettgca teggeggtga ggcc 474 <210> 325 <211> 532 <212> DNA

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<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(532)
      <223> n = A, T, C or G
      <400> 325
gaggagacag gacagagcgt ctggagaggc aggaggacac cgagttcccc gtgttggcct
                                                                        60
ccaggtcctg tgcttgcgga gccgtccggc ggctgggatc gagccccgac aatgggcaac
                                                                       120
gcgcaggagc ggccgtcaga gactatcgac cgcgagcgga aacgcctggt cgagacgctg
                                                                       180
caggeggaet egggaetget qttggaegeg etgetggege ggggegtget eacegggeea
                                                                       240
gagtacgagg cattggatgc actgcctgat gccgagcgca gggtgcgccg cctactgctg
                                                                       300
ctggtgcagg gcaagggcga ggccgcctgc caggagctgc tacgctgtgc ccagcgtacc
                                                                       360
gegggegege eggaeeeege ttgggaetgg cageaeqtgg gteegggeta eegggaeege
                                                                       420
agctatgacc ctccatgccc aggccactgg acgccggagg cacccggctc ggggaccaca
                                                                       480
tgccccgggt tgcccagact tcagaccctg acgaggncgg gggccctgag gg
                                                                       532
      <210> 326
      <211> 322
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(322)
      <223> n = A, T, C or G
      <400> 326
caaaattaac attttatta aatcaagtta aaaaaaatgt tcagtgtana aaagtcaaca
                                                                        60
agggttttaa caaaaccaaa atataccttt ttatacaata tatgtatata ttagcagcaa
                                                                       120
actacttctg anattctctt tcttttatgt tcttctagtt attttaaaga aagcataaac
                                                                       180
aatgtatatt agtatggaat gtcagcaaat ccactcttag tcctttattc tgtgatttgg
                                                                       240
gccttctaca aaatactttg tgattctcac taatgaatat taagaacata cccaatttta
                                                                       300
actadaaagt agtgaaacag tg
                                                                       322
      <210> 327
      <211> 387
      <212> DNA
      <213> Homo sapien
      <400> 327
aaaaccgtgt actattagcc atggtcaacc ccaccgtgtt cttcgacatt gccgtcgacg
                                                                        60
gcgagccctt gggccgcgtc tcctttgagc tgtttgcaga caaggtccca aagacagcag
                                                                       120
aaaattttcg tgctctgagc actggagaga aaggatttgg ttataagggt tcctgctttc
                                                                       180
acagaattat tccagggttt atgtgtcagg gtggtgactt cacacgccat aatggcactg
                                                                       240
gtggcaagtc catctatggg gagaaatttg aagatgagaa cttcatccta aagcatacgg
                                                                       300
gtcctggcat cttgtccatg gcaaatgctg gacccaacac aaatggttcc cagtttttca
                                                                       360
tctgcactgc caagactgag tggttgg
                                                                       387
      <210> 328
      <211> 502
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(502)
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<223> n = A, T, C or G<400> 328 ageageeegg egeggeegee gegeeggegg geggeaagge teegggeeag eatggggget 60 120 tegtggtgae tgteaageaa gagegeggeg agggteeaeg egegggegag aaggggteee acgaggagga gccggtgaag aaacgcggct ggcccaaggg caagaagcgg aagaagattc 180 tgccgaatgg gcccaaggca ccggtcacgg gctacgtgcg cttcctgaac gagcggcgcg 240 agcagateeg caegegeeac eeggatetge eettteeega gateaceaag atgetgggeg 300 ccgagtggag caagctgcag ccaacggaaa agcagcggta cctggatgag qccnagagag 360 420 agaagcagca gtacatgaag gagctgcggg cgtaccagca gtctgaagcc tataagatgt gcacggagaa gatccaggag aagaagatca agaaagaaga ctcgagctct gggctcatga 480 acactcttct gaatggacac aa 502 <210> 329 <211> 463 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(463) <223> n = A, T, C or G<400> 329 caagttgcac attttaattt acaattttta ccaataaaaa ggattagttt acaaaaaggg 60 aagteettta tacaaaataa qqacaatttq taaaqanaat ecaetqteat qttttqeett 120 gtcaagtcaa aactcaaata gcttgttttg gtaaaattat tccagaaaca taatccagac 180 aaaatcaata acgtcatcag cttcctaacc atgtttaana ggaataactt catgaacatt 240 ttgccctgaa ctgaanagtt ctaaatactt gtaaaccttt aggaaaaaat gactgctcgc 300 aggcagcttg actggtaaga gggtacacca nagactccgg gtcactcact gtcagaatat 360 tettatacat acaatgagte tecacgeetg tacaatgagt gtegtgeaac ataattggag 420 taatggcctc taaaatttta caagtaaact ttattgnggc ccc 463 <210> 330 <211> 500 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(500) <223> n = A,T,C or G<400> 330 taattataga totacaaaat atgaaatgta ttocaagaat goagaaaaac catotagaag 60 caaaaggact ataaaacaaa aacagagaag aaaattcatg gctaaaccag ctgaagaaca 120 gettgatgtg ggacagteta aagatgaaaa catacataca teacatatta eecaagaega 180 atttcaaaga aattcagaca gaaatatgga agagcatgaa gagatgggaa atgattgtgt 240 ttccaaaaaa acagatgcca cctgtgggaa gcaagaaaag tagcactaga aaagataagg 300 aagaatctaa aaagaagcgc ttttccagtg agtccaagaa caaacttgtn cctgaagaag 360 tgacttcaac tgtcacgaaa agtcgaanaa tttccangcg tccatctgat tggtgggtgg 420 taaaancaga ggagagteet gtttatagea attetteagt aagaaatgaa ttaccaantg 480 catcacaatn ntgcccggaa 500 <210> 331 <211> 494 <212> DNA <213> Homo sapien

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<220>
      <221> misc feature
     <222> (1)...(494)
     <223> n = A, T, C or G
      <400> 331
tctctctctc tctcaaaatt acagtgttca ttgtcattga cctcagcagc aaatttgact
                                                                      60
tgaattcact taggatcgca ggaatcaggg gaaagtgatt ttaaaggtgg tttctccagc
                                                                     120
acattttaag aaaagggacc aaaagttatt ttagcttcct caatagattg catgttgctt
                                                                     180
attaggataa taaattaata ttaaatgcaa tatatgtctt gnctttatta tggcatctat
                                                                     240
ttaggagttg ttcaaatcac tgcagtaggg ctctgcaaat aaaataatgn aacctattat
                                                                     300
catggatcta atgnactgna actttatcag tgaaaggnaa aatctcaaat aacaagtaca
                                                                     360
aacattggac aattacctat aaagatttgt aaaaggaaaa tttttccata gatttcattc
                                                                     420
ttggcatttt gtaaagacga ccctgcagnc ccctgtttgn aactttttta ataaaataga
                                                                     480
catctgttta cttg
                                                                     494
     <210> 332
     <211> 538
      <212> DNA
     <213> Homo sapien
     <400> 332
                                                                      60
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gggataggaa atagtgacca agaaatgcag cagctaaact tggaaggaaa gaactattgc
                                                                     120
acagecaaaa cattgtatat atetqaetea qacaaqeqaa ageaetteat qttqtetqta
                                                                     180
aagatgttct atggcaacag tgatgacatt ggtgtgttcc tcagcaagcg gataaaagtc
                                                                     240
atctccaaac cttccaaaaa gaagcagtca ttgaaaaatg ctgacttatg cattgcctca
                                                                     300
ggaacaaagg tggctctgtt taatcgacta cgatcccaga cagttagtac cagatacttg
                                                                     360
catgtagaag gaggtaattt tcatgccagt tcacagcagt ggggagcctt ttttattcat
                                                                     420
ctcttggatg atgatgaatc agaaggagaa gaattcacag tccgagatgg ctacatccat
                                                                     480
tatggacaaa cagtcaaact tgtgtgctca gttactggca tggcactccc aagattga
                                                                     538
     <210> 333
     <211> 499
     <212> DNA
     <213> Homo sapien
     <400> 333
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                                                                      60
120
catctcactc tcctatccca tcatctatgt ccaatatgag atctaggtca ctttcacctt
                                                                     180
tgattggatc agagactcta ccttttcatt ctggaggaca gtggtgtgag caagttgaga
                                                                     240
ttgcagatga aaacaatatg cttttggact atcaagacca taaaggagct gattcacatg
                                                                     300
caggagttag atatattaca gaggccctca ttaaaaaaact tactaaacag gataatttqq
                                                                     360
ctttqataaa atctctgaac ctttcacttt ctaaagacgg tggcaagaaa tttaagtata
                                                                     420
ttgagaattt ggaaaaatgt gttaaacttg aagtactgaa tctcagctat aatctaatag
                                                                     480
ggaagattga aaagtcgga
                                                                     499
     <210> 334
     <211> 561
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(561)
     <223> n = A, T, C or G
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<400> 334
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                                                                        60
gaaaattcaa tgaatcaagt gaaactcttg aaaaaggatc caggaaacga agtgaagcta
                                                                       120
aaactctacg cgctatataa gcaggccact gaaggacctt gtaacatgcc caaaccaggt
                                                                       180
gtatttgact tgatcaacaa ggccaaatgg gacgcatqga atgcccttgg cagcctgccc
                                                                       240
                                                                       300
aaggaagctg ccaggcagaa ctatgtggat ttggtgtcca gtttgagtcc ttcattggaa
tcctctagtc aggtggagcc tggaacagac aggaaatcaa ctgggtttga aactctggtg
                                                                       360
gtgacctccg aagatggcat cacaaagatc atqttcaacc cqqcccaaaa aqaaaaatgc
                                                                       420
cataaacact gagatgtatc atgaaattat gcgtgcactt aaagctgcca gcaaggatga
                                                                       480
ctcaatcatc actgttttaa cangaaatgg tgactattac agtagtggga atgatctgac
                                                                       540
taacttcnct gatattcccc c
                                                                       561
      <210> 335
      <211> 551
      <212> DNA
      <213> Homo sapien,
      <400> 335
aagctggtca tggctgggga gaccaccaac tecegeggee ageggetgee eeagaaggga
                                                                        60
gacgtggaga tgctgtgcgg cgggccgccc tgccagggct tcagcggcat gaaccgcttc
                                                                       120
aattegegea eetaeteeaa gtteaaaaae tetetggtgg ttteetteet eagetaetge
                                                                       180
gactactacc ggccccggtt cttcctcctg gagaatgtca ggaactttgt ctccttcaag
                                                                       240
                                                                       300
egetecatgg teetgaaget caeceteege tgeetggtee geatgggeta teagtgeace
ttcggcgtgc tgcaggccgg tcagtacggc gtggcccaga ctaggaggcg ggccatcatc
                                                                       360
ctggccgcgg cccctggaga gaageteeet ctgtteccgg agecactgea cgtgtttget
                                                                       420
ccccgggcct gccagctgag cgtggtgggt ggatgacaag aagtttgtga gcaacataac
                                                                       480
caggttgage tegggteett teeggaceat aeggtgegag aaacgatgte egacetgeeg
                                                                       540
                                                                       551
gaagtgcgga a
      <210> 336
      <211> 540
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
     <222> (1)...(540)
     <223> n = A, T, C or G
      <400> 336
aggtctatgt ctactgaagg caataaacga ggaatgatcc agcttattgt tgcaaggaga
                                                                        60
ataagcaagt gcaatgaget gaagtcacct gggagccccc ctggacctga gctgcccatt
                                                                       120
gaaacagcgt tggatgatag agaacgaaga atttcccatt ccctctacag tgggattgag
                                                                       180
gggcttgatg aatcgcccag cagaaatgct gccctcagta ggataatggg taaataccag
                                                                       240
ctgtccccta cagtgaatat gccccaagat gacactgtca ttatagaaga tgacaggttg
                                                                       300
ccagtgette etecacatet etetgaceag teetetteea geteccatga tgatgtgggg
                                                                       360
tttgtgacgg cagatgctgg tacttgggcc aaggctgcaa tcagtgattc agccgactgc
                                                                       420
tetttgagte cagatgttga tecagttett getttteaac gaaaaaggat ttggaegtea
                                                                       480
                                                                       540
gaagtatgtc agaaaaacgc accaaagcaa ttttcanatg ccagtcaatt ggatttcgtt
      <210> 337
      <211> 422
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
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<222> (1)...(422)
      <223> n = A, T, C or G
      <400> 337
gcagcaggaa cagttacagc agcagcagca acagcagctg ttgcaacagc agcaggaaca
                                                                        60
attgcagcag caacaactgc agcctcctcc cctggagccc gaggaggagg aagaggtgga
                                                                       120
gctggagetc atgccggtgg acctggggtc agagcaggag ctggagcagc agcggcagga
                                                                       180
gttggagcgg cagcaggagc tggaacggca gcaggagcag cggcagctgc agctcaaact
                                                                       240
gcaggaggag ctgcagcagc tggagcaaca gctggagcag cagcagcaqc agctggagca
                                                                       300
gcaggaggtg cagctggagc tgaccccggt ggagctaggc gcccaqcagc aggaggtgca
                                                                       360
getggagetg acceegtge ageeggaget geagetggaa etggtgeean eeeaggggge
                                                                       420
                                                                       422
gg
      <210> 338
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(601)
      <223> n = A, T, C or G
      <400> 338
catcttacga acgctctatg atgtcttatg agcggtctat gatgtcccct atggctgaac
                                                                        60
gctctatgat gtcagcctac gagcgctcta tgatgtcagc ctacgagcgc tctatgatgt
                                                                       120
cccctatggc tgagcgctct atgatgtcag cttatgaacg ctccatgatg tcagcttatg
                                                                       180
aacgctccat gatgtcccca atggctgatc gatctatgat gtccatgggt gctgaccggt
                                                                       240
ctatgatgtc gtcatactct gctgctgacc ggtctatgat gtcatcgtac tctgcagctg
                                                                       300
accgatctat gatgtcatct tatactgctg atcgttcaat gatgtctatg gctgctgatt
                                                                       360
cttacaccga ttcttacact gacacatata cagaggcata tatggtgcca cctttgcctc
                                                                       420
ctgaagagcc cccaacaatg ccaccgttgc cacctgagga gccaccaatg acaccaccat
                                                                       480
tgcctnctga ggaaccaccc agagggtcca gcattgccca cttgagcagt cagcattaac
                                                                       540
cagcttgaaa atacttggcc ctacanangg tgccatcatt accatctgaa gagctgtatc
                                                                       600
                                                                       601
      <210> 339
      <211> 440
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(440)
      <223> n = A, T, C or G
      <400> 339
agagggagga ggcccaactg gtgatgctgc tgctgctgct gctgccgccq ccqccqcctc
                                                                        60
tattgctgat actctagtgg ggctggaagg gtggttccta ttcgcaccat cgccaaccag
                                                                       120
agacagaggg aaaaaaaaaa ccggcagcca ctgctqatgt tqqqttcqqa qqctqcatcc
                                                                       180
gacteggtea caaggaaaat ggatteagtt tgeatetete ceteetttaa acagettete
                                                                       240
cgggtctcag catggtatca aagcttgaaa gagaqaagac tcaaqaaqcq aaqaggattc
                                                                       300
gtgagctgga gcagcgcaag cacacqqtqc tqqtqacaqa actcaaaqcc aaqctccatq
                                                                       360
aggagaagat gaaggagctg caggctgtga gggagaacct tatcaagcag cacgacagga
                                                                       420
aatgtcaang acggtgaagg
                                                                       440
      <210> 340
      <211> 450
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<212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(450)
      <223> n = A, T, C or G
      <400> 340
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aggattcctc aggccgacca gtggaagtct tcaaacaaga gcctggtgga ggctctgggg
                                                                       120
ctggaagccg agggtgcagt tcctgagaca cagactttga ccggatggag taaggggttc
                                                                       180
attggcatgc acagggaaat gcaagtcaac cccatttcaa agcggatggg gcccatgact
                                                                       240
gtggtcagga tggacgcttc agtccagcca ggcccttttc ggaccctgct ccagtttctt
                                                                       300
tatacgggac aactggatga aaaggaaaag gatttggtgg gcctggctca gatcgcagag
                                                                       360
gtcctcgaga tgttcgattt gaggatgatg gtggaaaaca tcatgaacaa ggaagccttc
                                                                       420
atgaaccagg agattacgaa nncctttcac
                                                                       450
      <210> 341
      <211> 451
      <212> DNA
      <213> Homo sapien
      <400> 341
aacagctatt aaaacagaaa atggatgaac ttcataagaa gttgcatcag gtggtggaga
                                                                        60
cateceatga ggatetgeec getteecagg aaaggteega ggttaateca geacgtatgg
                                                                       120
ggccaagtgt aggctcccag caggaactga gagcgccatg tcttccagta acctatcagc
                                                                       180
agacaccagt gaacatggaa aagaacccaa gagaggcacc teetgttgtt ceteetttgg
                                                                       240
caaatgctat ttctgcagct ttggtgtccc cagccaccag ccagagcatt gctcctcctg
                                                                       300
ttcctttgaa agcccagaca gtaacagact ccatgtttgc agtggccagc aaagatgctg
                                                                       360
gatgtgtgaa taagagtact catgaattca agccacagag tggagcagag atcaaagaag
                                                                       420
ggtgtgaaac acataaggtt gccaacacaa g
                                                                       451
      <210> 342
      <211> 498
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(498)
     <223> n = A,T,C or G
      <400> 342
ctcaagcagg ctattgaaga ggaaggaggc gatccagata atattgaatt aactgtttca
                                                                        60
actgatactc caaacaagaa accaactaaa qqcaaaggta aaaaacatga aqcagatgag
                                                                       120
ttgagtggag atgcttctgt gggaagatga tgcttttatc aaggactgtg aattggagaa
                                                                       180
tcaagaggca catgagcaag atggaaatga tgaactaaag gactctgaag aatttggtga
                                                                       240
aaatgaagaa gaaaatgtgc attccaagga gttactctct gcagaagaaa acaagagagc
                                                                       300
tcatgaatta atagaggcag aaggaataga agatatagaa aaagaggaca tcgaaagtca
                                                                       360
ggaaattgaa gctcaagaag gtgaagatga tacctttcta acagcccaag atggtgagga
                                                                       420
agaagaaaat gagaaagata tagcagggtt ctggtgatgg cncacaagaa gtatntaaac
                                                                       480
                                                                       498
ctcttccttc aaaaaggg
      <210> 343
     <211> 491
      <212> DNA
      <213> Homo sapien
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```
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                                                                       120
cctttttccg ctatatgcgg cagcagtgca tcaagcagga gctaatctqc aaqtqqatcq
                                                                       180.
accccqaqca actqaqcaat cccaaqaaqa qctqcaacaa aactttcaqc accatqcacq
                                                                       240
agctggtgac acacgtctcg gtggagcacg tcggcggccc ggaqcagagc aaccacgtct
                                                                       300
qcttctqqqa qqaqtqtccq cqcqaqqqca aqcccttcaa qqccaaatac aaactqqtca
                                                                       360
accacatecg cgtgcacaca ggcgagaaac ccttccctqc ccttccgggt gtggcaaagt
                                                                       420
cttcgcqcgc tccgagaacc tcaagatcca caaaaggacc acacagggga gaagccgtcc
                                                                       480
agtggagttg a
                                                                       491
      <210> 344
      <211> 412
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc feature
      <222> (1)...(412)
      \langle 223 \rangle n = A,T,C or G
      <400> 344
gtgcgctgtc ttcccgcttg cgtcagggac ctgcccgact cagtgqccqc catggcatca
                                                                        60
gatgaaggca aactttttgt tggagggctg agttttgaca ccaatgagca gtcgctggag
                                                                       120
caggitettet caaagtacgg acagatetet gaagtggtgg tigtgaaaga cagggagace
                                                                       180
cagagatete ggggatttgg gtttgtcace tttgagaaca ttgacgacge taaggatgee
                                                                       240
atgatggcca tgaatgggaa gtctgtagat ggacggcaga tccgagtaga ccaggcaggc
                                                                       300
aagtcgtcan acaaccgatc ccgtgggtac cgtggtggct ctgccggggg ccggggcttc
                                                                       360
ttccgtgggg gcccgangac ggggcccgtg ggttctctaa aagaagaggg ga
                                                                       412
      <210> 345
      <211> 498
      <212> DNA
      <213> Homo sapien
      <400> 345
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gacgtccgcc gggcacggga gggggccaag atgccgatca ataaatcaga gaagccagaa
                                                                       120
agctgcgata atgtgaaggt tgttgttagg tgccggcccc tcaatgagag agagaaatca
                                                                       180
atgtgctaca aacaggctgt cagtgtggat gagatgaggg gaactatcac tgtacataag
                                                                       240
actgattett ccaatgaace tecaaagaca tttaettttg atactgtttt tggaccagag
                                                                       300
agtaaacaac ttgatgttta taacttaact gcaagaccta ttattgattc tgtacttgaa
                                                                       360
ggctacaatg ggactatttt tgcatatgga caaaccggaa caggcaaaac ttttaccatg
                                                                       420
gaaaggtgtc gagctattcc tgaacttaga ggaataattc cccaatttct ttgctcacaa
                                                                       480
tatttgggcc atatttgc
                                                                       498
      <210> 346
      <211> 427
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(427)
      <223> n = A, T, C or G
      <400> 346
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agatggcggt cgccgtgaga actttgcagg aacagctgga aaaggccaaa gagagtctta agaacgtgga tgagaacatt cgcaagctca ccgggcggga tccgaatgac gtgaggccca tccaagccag attgctggc ctttctggtc ctggtggagg tagaggacgt ggtagtttat tactgaggcg tggattctca gatagtggag gaggaccccc agccaaacag agagaccttg aaggggcagt cagtaggctg ggcggggagc gtcggaccag aagagaatca cgccaggaaa gcgacccgga ggatgatgat gttaaaaagc cagcattgca gtcttcannt gtagctacct cccaaagagc gcccacgta gagaccttat ccagggatca aaattttgga tgaaaaggg gaaagcc	60 120 180 240 300 360 420 427
<210> 347 <211> 280 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 347 cacagaaagt tetecgetec cagacatggg tecetegget teetgeeteg gaagegeage ageaggeate gtgggaaggt gaagagette cetaaggatg accegteeaa geeggteeae cteacageet teetgggata caaggetgge atgacteaea tegtgeggga agtegacagg cegggateea aggtgaacaa gaaggaggtg gtggaggetg tgaccattgt agagacacea cecatggtgg ttgtgggeat tgtgggetae gtggaaacee</pre>	60 120 180 240 280
<210> 348 <211> 411 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 348 caactatgat gtgcctgaaa aatgggcacg attctatact gcagaagtag ttcttgcatt ggatgcaatc cattccatgg gttttattca cagagatgtg aagcctgata acatgctgct ggataaatct ggacatttga agttagcaga ttttggtact tgtatgaaga tgaataagga aggcatggta cgatgtgata cagcggttgg aacacctgat tatatttccc ctgaagtatt aaaatcccaa ggtggtgatg gttattatgg aagagaatgt gactggtggt cggttggggt attttatac gaaatgcttg taggtgatac acctttttat gcagattctt tggttggaac ttacagtaaa attatgaacc attaaaaatt cacttacctt tcctgatgat a</pre>	60 120 180 240 300 360 411
<210> 349 <211> 408 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 349 gatgggcatc tctcgggaca actggcacaa gcgccgcaaa accgggggca agagaaagcc ctaccacaag aagcggaagt atgagttggg gcgcccagct gccaacacca agattggccc ccgccgcatc cacacagtcc gtgtgcgggg aggtaacaag aaataccgtg ccctgaggtt ggacgtgggg aatttctcct ggggctcaga gtgttgtact cgtaaaacaa ggatcatcga tgttgtctac aatgcatcta ataacgagct ggttcgtacc aagaccctgg tgaagaattg catcgtgctc atcgacagca caccgtaccg acagtggtac gagtcccact atgcgctgcc cctgggccgc aagaagggag ccaaactgac ttctgaggaa gaagaaaa</pre>	120 180 240 300 360 408
<210> 350 <211> 409 <212> DNA · <213> Homo sapien	
<400> 350 ggttccccca gctctgggta cccggctctg catcgcgtcg ccatgatggg ccatcgtcca gtgctcgtgc tcagccagaa cacaaagcgt gaatccggaa gaaaagttca atctggaaac atcaatgctg ccaagactat tgcagatatc atccgaacat gtttgggacc caagtccatg	60 120 180

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atgaagatgc ttttggaccc aatgggaggc attgtgatga ccaatgatgg caatgccatt
                                                                       240
ettegagaga tteaagteea geateeageg geeaagteea tgategaaat tageeggaee
                                                                       300
caggatgaag aggttggaga tgggaccaca tcagtaatta ttcttgcagg ggaaatgctg
                                                                       360
                                                                       409
tctgtagctg agcacttcct ggagcagcag atgcacccaa caggtgggg
      <210> 351
      <211> 226
      <212> DNA
      <213> Homo sapien
      <400> 351
aatcccaaac atataactga actcctcaca cccaattgga ccaatctatc accctataga
                                                                        60
agaactaatg ttagtataag taacatgaaa acatteteet eegeataage etgegteaga
                                                                       120
ttaaaacact gaactgacaa ttaacagccc aatatctaca atcaaccaac aagtcattat
                                                                       1.80
taccctcact gtcaacccaa cacaggcatg ctcataagga aaggtt
                                                                       226
      <210> 352
      <211> 410
      <212> DNA
      <213> Homo sapien
      <400> 352
gcggaggggc tggctgggca ggaggggttg gcggggcagc agggccgcgg ccatggggag
                                                                        60
cttgaaggag gagctgctca aagccatctg gcacgccttc accgcactcg accaggacca
                                                                       120
cagoggoaag gtotocaagt cocagotoaa ggtootttoo cataacotgt gcacggtgot
                                                                       180
gaaggtteet catgacecag ttgeeettga agageaette agggatgatg atgagggtee
                                                                       240
agtgtccaac cagggctaca tgccttattt aaacaggttc attttggaaa aggtccaaga
                                                                       300
caactttgac aagattgaat tcaataggat gtgttggacc ctctgtgtca aaaaaaacct
                                                                       360
cacaaagaat cccctgctca ttacagaaga agatgcattt aaaatatggg
                                                                       410
      <210> 353
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(380)
      <223> n = A, T, C or G
      <400> 353
gagtttattt agaaagtatc atagtgtaaa caaacaaatt gtaccacttt gattttcttg
                                                                        60
gaatacaaga ctcgtgatgc aaagctgaag ttgtgtgtac aagactcttg acagttgtgc
                                                                       120
ttctctagga ggntgggttt ttttaaaaaa agaattatct gngaaccata cgtgattaat
                                                                       180
aaagatttcc tttaaggcan aggctggtcn agatgctgct gttatcttct gcctcagaca
                                                                       240
gacagtataa gnggtcttgt ttctaagatt cctaccacca gttactttgg gccaagtatc
                                                                       300
cacatcccct tgcgtatggg aggngggtga anagtgttgg atgcaaagng gttattatgg
                                                                       360
gaagnagete natggtaaaa
                                                                       380
      <210> 354
      <211> 379
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(379)
      <223> n = A, T, C or G
```

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<400> 354
caacacatct ttattaaaca cctgaagtta ctgggaggag gccatgatgc tggacacact
                                                                        60
gtcaaagtca atcttctcca caatgttctt gggtttaatg ctctcttctt ggctacagan
                                                                       120
gaanatctgc cccgactngt cggcactcca gccgtatttg ctcatccaca cctttagctg
                                                                       180
qctqtccqac aganccccqa qcatntcqqc caqcaqccan cqqncaatqt qctqqtaaqt
                                                                       240
gatacccaca acatggcaga taaactttcg gacanagtct tcaaagccag ttataccttc
                                                                       300
caagaggtcc atgttttcat ccagggcttg ccanaagcct ggaaatggca ggtctccaac
                                                                       360
aggtccccca ggtacaaaa
                                                                       379
      <210> 355
      <211> 499
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(499)
      <223> n = A, T, C or G
      <400> 355
qtccaqaqct qctqqtqctc ccqttcccca qaccctaccc ctatccccaq tqqaqccqqa
                                                                        60
gtgcgggcgc gccccaccac cgccctcacc atggtgctgt tggcagcagc ggtctgcaca
                                                                       120
aaagcaggaa aggctattgt ttctcgacag tttgtggaaa tgacccgaac tcggattgag
                                                                       180
qqcttattaq caqcttttcc aaaqctcatq aacactqqaa aacaacatac qtttqttqaa
                                                                       240
acagagagtg taagatatgt ctaccaqcct atggagaaac tgtatatggt actgatcact
                                                                       300
accaaaaaca gcaacatttt agaagatttg gagaccctaa ggctcttctc aagagtgatc
                                                                       360
cctgaatatt gcgagcctta gaagagaatg aaatatctga gcactgnttt gatttgattt
                                                                       420
ttgcttttga tgaaaatgtc gcactgggat acccgggang aatgttaact tggcacagat
                                                                       480
canaaccttt cacagaaaa
                                                                       499
      <210> 356
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 356
gggcttctgc tgagggggca ggcggagctt gaggaaaccg cagataagtt ttttctctt
                                                                        60
tgaaagatag agattaatac aactacttaa aaaatatagt caataggtta ctaagatatt
                                                                       120
gcttagcgtt aagtttttaa cgtaatttta atagcttaag attttaagag aaaatatgaa
                                                                       180
gacttagaag agtagcatga ggaaggaaaa gataaaaggt ttctaaaaca tgacggaggt
                                                                       240
tgagatgaag cttcttcatg gagtaaaaaa tgtatttaaa agaaaattga gagaaaggac
                                                                       300
tacaqaqccc cqaattaata ccaataqaaq qqcaatqctt ttaqattaaa atqaaqqtqa
                                                                       360
cttaaacagc ttaaagttta ntttaaaagt tgtaggtgat taaaataatt tgaaggcgat
                                                                       420
cttttaaaaa gagattaaac ccgaaggtga ttaaaagacc ttgaaatcca tgacgccagg
                                                                       480
gagaattgcc gtcatttaaa gcctagttaa c
                                                                       511
      <210> 357
      <211> 511
      <212> DNA
      <213> Homo sapien
```

<220>

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<221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 357
gatacttcac atttccctag ggacgggagc ccgaggggtc cgttcggccc tcttcctctc
                                                                        60
gctgggccga caccccgctg taggaccgta acccttagtc ccaatgcctc cgtaagcgga
                                                                       120
gttgagtggg tgcctgtggt tggagctgtg gaggtgtccc cggtggcgag cgcqqccaqa
                                                                       180
actgcggtca cttaagtttt ccgtgtgcgg gttgcaagga gcgtgcgtgc gtctggtata
                                                                       240
atttggcttc ctgagattct gcttacaaga aaggagtggg aaataccctt ggaaagaaaa
                                                                       300
ctaaaacagt aagaaaacca aaacttattt ttacatggnt gtcagcacat ttaccgatat
                                                                       360
ggacactttt cccaataatt tcctcctggt ggagacagtg gattgacagg ttctcagtcg
                                                                       420
gaattocaga aaaatgttaa ttgatgaaaa gggtacnatg tgagcatcat aaagntaatt
                                                                       480
attaanacac tgaaggctga acacacaagg g
                                                                       511
      <210> 358
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(401)
      <223> n = A, T, C or G
      <400> 358
acggatgaag atgatgacct tcaagaaaat gaagacaata aacaacataa agaaagcttg
                                                                        60
aaaagagtga cctttgcttt accagatgat gcggaaactg aagatacagg tgttttaaat
                                                                       120
gtaaagaaaa attctgatga agttaaatcc tcctttgaaa aaagacagga aaagatgaat
                                                                       180
gaaaaaattg catctttaga aaaagagttg ttagaaaaaa agcccqtqqc agcttcagqq
                                                                       240
ggaagtgaca gcacagaaga ggccagagaa cacctcctgg aggagaccct acctttgcca
                                                                       300
tetgeeegat ggeeetgtga ttacagagga acceeettea etggagattt etttaaenga
                                                                       360
ngatagagat engnttggga tatqtntcct taagaaaacc t
                                                                       401
      <210> 359
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 359
gegatgeecg egegeecagg aegeeteete eegetgetgg eeeggeegge ggeeetgaet
                                                                        60
gegetgetge tgetgetget gggecatgge ggeggeggge getggggege eegggeeeag
                                                                       120
gaggcggcgg cggcggcgc ggacgggccc cccgcggcag acggcgagga cggacaggac
                                                                       180
cegeacagea ageacetgta caeggeegae atgtteaege aegggateea gagegeeege
                                                                       240
geacttegte atgttetteg egeeetggtg tggacaettg eeageggett geageegant
                                                                       300
ttggaatgac cttggganga acaaatacaa cagcatggaa agaatgccaa aagtctatgt
                                                                       360
ggnttaaagt ggacttgcac nggccacttc gactngtgct cccccaaggg gngggaagat
                                                                       420
acccacctta aaacttttca accaagccaa aaactttgaa aaccaggtct cggattcaaa
                                                                       480
atggaaaact gatgttcaac ctgaacaaga a
                                                                       511
      <210> 360
      <211> 511
      <212> DNA
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<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      \langle 223 \rangle n = A,T,C or G
      <400> 360
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                                                                         60
tagacagcaa gtttctaaaa cagcaaaaga aagatgtggt caaacggcaa gaagtaatat
                                                                        120
atgagttgat gcagacagag tttcatcatg tcccgactct caagatcatg agtggtgtgt
                                                                        180
cnagccnggg gatgatggcg gatctgnttt ttgagcanca gatggtagaa aaagctggtt
                                                                        240
ccctgtttgg atgagettga tcagtatece atacccatte tttecagagg attettggag
                                                                        300
ccggaaagaa nggagtcttc ttggtgggat aaaaagtgaa aaagaacttt ctcttcaana
                                                                        360
aggatagggg gatgtgcttt gtaaaatcan tttttcaggg ngganaatgc cnnaaccgtt
                                                                        420
ttaaagaaaa acatnttggg naagtttttg tgggccaaca ttacccggtc ttgtaaacct
                                                                        480
accttcaaag aacctttttg cccagggtta a
                                                                        511
      <210> 361
      <211> 411
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(411)
      <223> n = A, T, C or G
      <400> 361
gctcagcggc ccgatcccac ggaagcgcgc tcggaggggt gggacccggc cggaccggag
                                                                         60
atggcgccgc cagcgggcgg ggcggcggcg gcqqcctcqq acttqqqctc cqccqcaqtq
                                                                       120
ctcttggctg tgcacgccgc ggtgaggccg ctgggcgccg ggccagacgc cgaagcacaa
                                                                       180
cttgeggagg ctgeagetta acgeggaece tgagaageet ggegettnen getggaactt
                                                                        240
cttggcgcgg gacctggggc ggtaatttga gtggccctga gtcatttcta caccatccag
                                                                        300
gcccaccaca cgactaagct cacaagaagg ctgaactnnc tgattctnaa cctagaanta
                                                                        360
cgtgcatcta tcagtgccng aagaaatgac aacataccac tggcaactct g
                                                                        411
      <210> 362
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 362
egggggaeeg ggetgeettg geeeeteage getegegtet titteeggeag tiggaaeget
                                                                         60
tectgttgtc ctcaccegta accgectgtt geceectgtc teagagtece teaegegtee
                                                                        120
cctcccqtct ttqqctcqtt qgctqccqcc qccqqqqctt cqccaqcctt caaqtcqaqa
                                                                        180
ctactggccg aaggggcgtc tgcggctctc cgccgtcccc agccctgcct ctccctgggc
                                                                       240
tctgccatgg caatgacagg ctcaacacct tgctcatcca tgagtaacca cacaaaggaa
                                                                        300
agggtgacaa tgaccaaaag tgacactgga gaatttttat agcaacctta tcgctcacat
                                                                        360
gaagaacgag aaatgagaca aaagaagtta gaaaaagggg atggaagaag aaggcctaaa
                                                                        420
                                                                        480
aaaatgaagg agaaaaccaa cttccgaaga tcaaccacat tgcttcggaa anggaaacaa
aantttcttt cgtttgaaan aaaaacaaan a
                                                                        511
```

```
<210> 363
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 363
caggatetgg ggagaaagag ccccatecet tetetetetg ccaccattte ggacaccecg
                                                                        60
cagggacteq ttttqqqatt eqeactqact tcaaqqaaqq acqcqaacce ttctctqace
                                                                       120
ccagcteggg eggecacetg tetttgeege ggtgaceett eteteatgae eetgeggtge
                                                                       180
cttgagecet eegggaatgg eggggaaggg acgeggagee agtggggae egeggggteg
                                                                       240
qcqqaqqagc catccccgca gqcggcgcgt ctggcgaagg ccctgcggga gctcggtcag
                                                                       300
acaggatggt actggggaag tatgactgtt aatgaagcca aagagaaatt aaaagaggca
                                                                       360
ccagaaggaa ctttcttgat tagagatagc tcgcattcag a
                                                                       401
      <210> 364
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 364
agtcaaaggt ttcttttccc tttttaccat ggtttctaca aaaataacct tcaggaaaaa
                                                                        60
gaaaatcagg aaaaaaattt tttttcaata atcttattcc ctatattaaa ttagatttga
                                                                       120
agaggattaa cgttgtttta qtttqqqtcc aqatcaqcct tatacaacat ttctaaactc
                                                                       180
atttgtactt ttaaaaaatt taaacacaga cttctaaaat tacttgatgt aagtaattta
                                                                       240
aatcacttat gaccaagtta ttaaccttat gaatcagaag tctgaccctt gtaggaaatt
                                                                       300
atattcacat ataaagtaca tcagatcttt gccatatatt gatggttatt atgcataaac
                                                                       360
acattgagtt gtgttggaag cagatttata aacctgcatg t
                                                                       401
      <210> 365
      <211> 361
      <212> DNA
      <213> Homo sapien
      <400> 365
atctggagtt gcacaaatag ttctttagaa cataaaacta aatggattta tacataacag
                                                                        60
ttacattcag catttaagag aggcagtaca aaaatgtgtt ctgcttttat ctgatataaa
                                                                       120
ttgcatgtaa taccatgatt taaacaatat cagttatatt aactaatgcc atgagatata
                                                                       180
tcttactcag aacgtctgat gtttcccata atagacagaa aaaatgcagt tgtatqagca
                                                                       240
actgagtttc ttttcatctt caaattcatt tqtgatqqtq qqaaqatcta aqqacaatcc
                                                                       300
ttccattgaa qaagtaggaa aaacagttca gcactgttct gaactcatca aaaatgaaat
                                                                       360
                                                                       361
      <210> 366
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 366
cgggagcagc agaggtctag cagccgggcg ccgcgggccg ggggcctgag gaggccacag
                                                                        60
gacgggegte tteceggeta gtggageeeg gegeggggee egetgeggee geacegtgag
                                                                       120
gggaggagge cgaggaggac gcagcgccgg ctgccggcgg gaggaagcgc tccaccaggg
                                                                       180
                                                                       240
cccccgacgg cactcgttta accacatccg cgcctctgct ggaaacgctt gctggcgcct
gtcaccggtt ccctccattt tgaaagggaa aaaggctctc cccacccatt ccctqcccc
                                                                       300
taggagetgg ageeggagga geegegetea tggegtteag eeegtggeag atcetgteee
                                                                       360
ccgtgcagtg ggcgaaatgg acgtggtctg cggtacgcgg c
                                                                       401
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<211> 401
      <212> DNA
      <213> Homo sapien
      <400> 367
catggagtcg ggcaagatgg cgcctcccaa gaacgctccg agagatgcct tggtgatggc
                                                                        60
acagatectg aaggatatgg gaateacaga gtatgaacca agggttataa ateaaatgtt
                                                                       120
ggaatttgct ttccgttatg tgactacaat tctggatgat gcaaaaattt attcgagcca
                                                                       180
                                                                       240
tgctaagaaa cctaatgttg atgcagatga tgtgagactg gcaatccagt gtcgtgctga
                                                                       300
ccaatctttt acctctcctc ccccaagaga ttttttactg gatatcgcaa ggcagaaaaa
tcaaacccct ttgccactga ttaagccata tgcaggacct agactgccac ctgatagata
                                                                       360
ctgcttaaca gctccaaact ataggctgaa gtccttaatt a
                                                                       401
      <210> 368
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 368
cggagcggta ggagcagcaa tttatccgtg tgcagcccca aactggaaag aagatgctaa
                                                                        60
ttaaagtgaa gacgctgacc ggaaaggaga ttgagattga cattgaacct acagacaagg
                                                                       120
                                                                       180
tggagcgaat caaggagcgt gtggaggaga aagagggaat cccccacaa cagcagaggc
teatetacag tggcaageag atgaatgatg agaagacage agetgattae aagattttag
                                                                       240
gtggttcagt ccttcacctg gtgttggctc tgagaggagg aggtggtctt aggcagtgat
                                                                       300
ggaccctcca ttttacctct ttaccctgtc gctcataatg aggcatcata tatcctctca
                                                                       360
ctctctggga caccatagcc ctgcccctc ccctggatgc c
                                                                       401
      <210> 369
      <211> 174
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(174)
      <223> n = A, T, C or G
      <400> 369
gcgagnnggg cgccaagcgc ggggccggag cggccttccc ggagtccttt gcgcggcacc
                                                                        60
                                                                       120
tggcgacaaa atggctgccc gagggagacg ggcggagcct cagggccggg aggctccggg
                                                                       174
ccccgcgggc ggtggcggtg gcgggagccg ttgggctgag tcgggatcgg ggac
      <210> 370
      <211> 375
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(375)
      <223> n = A, T, C or G
      <400> 370
tgcttttcca actttattta gaaaaacaaa tccaggtccc agtgccccct gtaccctccc
                                                                        60
cgaccccagc cataatttaa ataacttana gacagagttg gagggagggg acagganagg
                                                                       120
ttggggtcac ggtggaagga ggaaganagc ccactacagc cgccgcagcg cccgcttctt
                                                                       180
gtccgtcttt ttcttggccg ccagcttctt atcgcgctcg ccagcatgct tnttggccat
                                                                       240
                                                                       300
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Gly His Arg Pro Val Leu Val Leu Ser Gln Asn Thr Lys Arg Glu Ser
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Gly Arg Lys Val Gln Ser Gly Asn Ile Asn Ala Ala Lys Thr Ile Ala
                            40
Asp Ile Ile Arg Thr Cys Leu Gly Pro Lys Ser Met Met Lys Met Leu
                        55
Leu Asp Pro Met Gly Gly Ile Val Met Thr Asn Asp Gly Asn Ala Ile
                    70
                                        75
Leu Arg Glu Ile Gln Val Gln His Pro Ala Ala Lys Ser Met Ile Glu
                85
                                    90
Ile Ser Arg Thr Gln Asp Glu Glu Val Gly Asp Gly Thr Thr Ser Val
                               105
                                                   110
Ile Ile Leu Ala Gly Glu Met Leu Ser Val Ala Glu His Phe Leu Glu
                           120
                                               125
Gln Gln Met His Pro Thr Val Val Ile Ser Ala Tyr Arg Lys Ala Leu
                       135
                                           140
Asp Asp Met Ile Ser Thr Leu Lys Lys Ile Ser Ile Pro Val Asp Ile
                   150
                                       155
Ser Asp Ser Asp Met Met Leu Asn Ile Ile Asn Ser Ser Ile Thr Thr
                                   170
Lys Ala Ile Ser Arg Trp Ser Ser Leu Ala Cys Asn Ile Ala Leu Asp
           180
                               185
                                                   190
Ala Val Lys Met Val Gln Phe Glu Glu Asn Gly Arg Lys Glu Ile Asp
                           200
                                               205
Ile Lys Lys Tyr Ala Arg Val Glu Lys Ile Pro Gly Gly Ile Ile Glu
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                       215
                                           220
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Asp Ser Cys Val Leu Arg Gly Val Met Ile Asn Lys Asp Val Thr His 230 Pro Arg Met Arg Arg Tyr Ile Lys Asn Pro Arg Ile Val Leu Leu Asp 250 Ser Ser Leu Glu Tyr Lys Lys Gly Glu Ser Gln Thr Asp Ile Glu Ile 265 Thr Arg Glu Glu Asp Phe Thr Arg Ile Leu Gln Met Glu Glu Glu Tyr 280 Ile Gln Gln Leu Cys Glu Asp Ile Ile Gln Leu Lys Pro Asp Val Val 295 300 Ile Thr Glu Lys Gly Ile Ser Asp Leu Ala Gln His Tyr Leu Met Arq 310 315 Ala Asn Ile Thr Ala Ile Arg Arg Val Arg Lys Thr Asp Asn Asn Arg 330 Ile Ala Arg Ala Cys Gly Ala Arg Ile Val Ser Arg Pro Glu Glu Leu 345 Arg Glu Asp Asp Val Gly Thr Gly Ala Gly Leu Leu Glu Ile Lys Lys 360 Ile Gly Asp Glu Tyr Phe Thr Phe Ile Thr Asp Cys Lys Asp Pro Lys 375 380 Ala Cys Thr Ile Leu Leu Arg Gly Ala Ser Lys Glu Ile Leu Ser Glu 390 395 Val Glu Arg Asn Leu Gln Asp Ala Met Gln Val Cys Arg Asn Val Leu 405 410 Leu Asp Pro Gln Leu Val Pro Gly Gly Gly Ala Ser Glu Met Ala Val 420 425 Ala His Ala Leu Thr Glu Lys Ser Lys Ala Met Thr Gly Val Glu Gln 440 445 Trp Pro Tyr Arg Ala Val Ala Gln Ala Leu Glu Val Ile Pro Arg Thr 455 460 Leu Ile Gln Asn Cys Gly Ala Ser Thr Ile Arg Leu Leu Thr Ser Leu 470 475 Arg Ala Lys His Thr Gln Glu Asn Cys Glu Thr Trp Gly Val Asn Gly 485 490 Glu Thr Gly Thr Leu Val Asp Met Lys Glu Leu Gly Ile Trp Glu Pro 500 505 Leu Ala Val Lys Leu Gln Thr Tyr Lys Thr Ala Val Glu Thr Ala Val 520 Leu Leu Arg Ile Asp Asp Ile Val Ser Gly His Lys Lys Gly 535 Asp Asp Gln Ser Arg Gln Gly Gly Ala Pro Asp Ala Gly Gln Glu

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<211> 307

<212> PRT

<213> Homo sapiens

<400> 397

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Gly Phe His Met Thr Trp Ser Val Lys Leu Asp Glu His Ile Ile Pro
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                                    90
Leu Gly Ser Met Ala Ile Asn Ser Ile Ser Lys Leu Thr Gln Leu Thr
           100
                               105
                                                   110
Gln Ser Ser Met Tyr Ser Leu Pro Asn Ala Pro Thr Leu Ala Asp Leu
                           120
                                               125
Glu Asp Asp Thr His Glu Ala Ser Asp Asp Gln Pro Glu Lys Pro His
   130
                       135
                                           140
Phe Asp Ser Arg Ser Val Ile Phe Glu Leu Asp Ser Cys Asn Gly Ser
                   150
                                       155
Gly Lys Val Cys Leu Val Tyr Lys Ser Gly Lys Pro Ala Leu Ala Glu
                                   170
Asp Thr Glu Ile Trp Phe Leu Asp Arg Ala Leu Tyr Trp His Phe Leu
           180
                               185
Thr Asp Thr Phe Thr Ala Tyr Tyr Arg Leu Leu Ile Thr His Leu Gly
                           200
Leu Pro Gln Trp Gln Tyr Ala Phe Thr Ser Tyr Gly Ile Ser Pro Gln
                       215
                                           220
Ala Lys Gln Trp Phe Ser Met Tyr Lys Pro Ile Thr Tyr Asn Thr Asn
                   230
                                       235
Leu Leu Thr Glu Glu Thr Asp Ser Phe Val Asn Lys Leu Asp Pro Ser
               245
                                   250
Lys Val Phe Lys Ser Lys Asn Lys Ile Val Ile Pro Lys Lys Gly
           260
                               265
                                                   270
Pro Val Gln Pro Ala Gly Gly Gln Lys Gly Pro Ser Gly Pro Ser Gly
                           280
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Pro Ser Thr Ser Ser Thr Ser Lys Ser Ser Ser Gly Ser Gly Asn Pro
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Thr Arg Lys
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 <211> 410
 <212> DNA
 <213> Homo sapiens
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 cgcaaccatg agcagegagg cegagaceca gcagecgece geegeeeeee eeegeegeee 180
 cegeceteag egeegeegae accaageeeg geactaeggg eageggegea gggageggtg 240
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 <211> 433
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 gatacteete acetgeteet tgaatgacag egecacagag gteacaggge acegetgget 180
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 <212> DNA
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tccagatatg tctgt
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<211> 416
<212> DNA
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<400> 404
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taactagaaa taactttgca aggagagcca aagctaagac ccccgaaacc agacgagcta 240
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<213> Homo sapiens
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<210> 410
<211> 423
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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acaggaagge tteggetgeg tggtcaccaa ecgattegae eagttatttg acgaegaate 180
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429
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			Leu 500					505					510		
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GLy 545	тте	ьeu	Ser	LLO	550	ьeu	Asp	тÀг	мet	Val 555	Thr	qsa	GΤΆ	Ala	11e 560

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ser	Ser 101(		Thr	Thr	ASN	Asn 101		Pro	туr	Ala	Lys 102(		Pro	Asp	Thr

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ser tro ser wan	2005	20:		2015	
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Leu Lys His Val		Gln Ser Me	t Val Gln Ly		Glu
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Gly Lys Lys Ly 20 Ser Thr Lys Al	60		2665	,		2670	)	
2675			2680		2	685		
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Pro Tyr Val Gln Asp Ile His Ser Val Gly Ser Leu Cys Lys Leu Tyr
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Phe Arg Glu Leu Pro Asn Pro Leu Leu Thr Tyr Gln Leu Tyr Glu Lys
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Phe Ser Asp Ala Val Ser Ala Ala Thr Asp Glu Glu Arg Leu Ile Lys
                                     90
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Ile His Asp Val Ile Gln Gln Leu Pro Pro Pro His Tyr Arg Thr Leu
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                                                    110
Glu Phe Leu Met Arg His Leu Ser Leu Leu Ala Asp Tyr Cys Ser Ile
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                                                125
Thr Asn Met His Ala Lys Asn Leu Ala Ile Val Trp Ala Pro Asn Leu
    130
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Leu Arg Ser Lys Gln Ile Glu Ser Ala Cys Phe Ser Gly Thr Ala Ala
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Phe Met Glu Val Arg Ile Gln Ser Val Val Val Glu Phe Ile Leu Asn
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170

His Val Asp Val Leu Phe Ser Gly Arg Ile Ser Met Ala Met Gln Glu

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Lys	Arg 290	Lys	Leu	Gln	Arg	Asn 295	Glu	Ser	Glu	Pro	Ser 300	Glu	Met	Lys	Ala
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Pro 385	Ala	Leu	Met	Ser	Pro 390	His	Ser	Ala	Glu	Asp 395	Val	Asp	Leu	Ser	Pro 400
Pro	Asp	Ile	Gly	Val 405	Ala	Ser	Leu	Asp	Phe 410	Asp	Pro	Met	Ser	Phe 415	Gln
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			Asp	485					490					495	
			Glu 500	_			_	505				-	510	_	-
		515	Lys				520		•			525			
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		595	Ala				600					605			
	610		Ser			615					620				
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Ser	Val	Ser	Leu	Ile	Pro	Pro	Pro	Pro	Pro	Pro	Lys	Asn	Val	Ala	Arg

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		_		Asn 805					810				_	815	_
			820	Arg				825					830		
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	850			Pro		855			_	_	860	_			
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		995		Leu			1000	)				100	5		
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102	วี			Pro	1030	)				1035	5				1040
				Ser 1045	5		_		1050	)				1055	õ
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		107	5	Pro			1080	)				108	õ		
	109	)		Arg		1095	õ			•	110	)			
Asn	Cys	Leu	His	Phe	Asn	Met	Thr	Pro	Asn	Cys	Gln	Tyr	Arg	Pro	G1n

1105				1115	~ 7		_	1120
Ser Val Pro Pro 1		_			G⊥n		-	_
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1140			1145	II - C	T	1150		Q
Val Ala Pro Gly	arg Asn A		_	HIS Ser	_		Cys	ser
1155	37-3 0 0	1160		C	1165		m1-	Q
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Tyr Pro Glu Asp			Dro Thr	1180		775.7	Cln	Cox
1185	1190	ero răr	LTO THE	1195	Arg	Val	GTII	1200
Leu His Ala Pro		Sor Mot	Tlo 7rc		Dro	Tlo	C02	
	1205 1205	Ser Wer	1210		ETO		1215	_
Thr Glu Val Pro		Asn Glu			Pro			
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Tyr Gln Tyr Lys				Ala Arg	Ser			His
1235		1240			1245	_		
Val Thr Gln Leu	Gln Pro T			Glv Arg			Tvr	Ara
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Tyr Ser Pro Tyr	Ser Ser S	Ser Ser	Ser Ser	Tyr Tyr	Ser	Pro	Asp	Gly
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Ala Leu Cys Asp	Val Asp <i>R</i>	Ala Tyr	Gly Thr	Val Gln	Leu	Arg	Pro	Leu
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His Arg Leu Pro A	Asn Arg <i>F</i>	Asp Phe	Ala Phe	Tyr Asn	Pro	Arg	Leu	Gln
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1330	]	1335		1340	)			
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Arg Gln Lys Val :  Arg Gln Lys Val :  1380 Pro Ala Val Gln :  1395 Ser Lys Ser Asp :  1410 Lys Glu Ser Arg :  1425 Arg Phe Tyr Arg :  His Gly Gly His G  1460 Lys Gln Ser Ser :  1475 Leu Pro Glu His :  1490 Glu Ser Lys Asn G	Asp Val I 1350 Tyr Arg M 1365 Lys Gly I Asp Asp I Pro Gly I His Ala A 1430 Arg His I 1445 Gly Ser I Leu Arg S Arg Ala I Gly Pro I 1510	Lys His  Met Gln  Pro Val  Leu Gly 1400  Lys Thr  1415  Ala Lys  Pro Glu  Thr Gln  Ser Arg 1480  His Gln  1495  Pro Tyr	Ser Ile 1370 Met Ser 1385 Gly Ile Gly Leu Ala Ile Ala Glu 1450 Pro Glu 1465 Lys Leu Glu Ala Pro Gln	Thr Ser 1355 Arg Arg Gln Tyr Tyr Val Leu Ser 1420 Ser Pro 1435 Met Asp Lys Pro Pro Asp Ser His 1500 Gly Ala 1515	Trp Glu Asp Ile 1405 Val Glu Arg Ser Met 1485 Arg Gly	Asn 1390 His Ala Gly Ala Leu 1470 Gly Gln	Arg 1375 Met Leu Glu Glu His 1455 Pro Cys Phe Leu	1360 Ala Thr Arg Gly Asp 1440 His Gln Ser Cys Asp 1520
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Asp Met Glu Lys 'Asp Met Glu Lys 'Asp Met Glu Lys 'Asso Isso Isso Isso Isso Isso Isso Isso	Asp Val I 1350 Tyr Arg M 1365 Lys Gly F Asp Asp I Pro Gly I His Ala F 1430 Arg His F 1445 Gly Ser T Leu Arg S Arg Ala F Gly Pro F 1510 Gly Ile F	Lys His Met Gln Pro Val Leu Gly 1400 Lys Thr 1415 Ala Lys Pro Glu Thr Gln Ser Arg 1480 His Gln 1495 Pro Tyr Pro Asp	Ser Ile 1370 Met Ser 1385 Gly Ile Gly Leu Ala Ile Ala Glu 1450 Pro Glu 1465 Lys Leu Glu Ala Pro Gln Thr Ser 1530	Thr Ser 1355 Arg Arg Gln Tyr Tyr Val Leu Ser 1420 Ser Pro 1435 Met Asp Lys Pro Pro Asp Ser His 1500 Gly Ala 1515 Glu Pro	Trp Glu Asp Ile 1405 Val Glu Arg Ser Met 1485 Arg Gly Val	Asn 1390 His Ala Gly Ala Leu 1470 Gly Gln Gln Ser	Arg 1375 Met Leu Glu Glu His 1455 Pro Cys Phe Leu Tyr 1535	1360 Ala Thr Arg Gly Asp 1440 His Gln Ser Cys Asp 1520 His
Arg Gln Lys Val  Arg Gln Lys Val  1380 Pro Ala Val Gln  1395 Ser Lys Ser Asp  1410 Lys Glu Ser Arg  1425 Arg Phe Tyr Arg  His Gly Gly His G  1460 Lys Gln Ser Ser  1475 Leu Pro Glu His 1  1490 Glu Ser Lys Asn  1505 Tyr Gly Ser Lys  Asn Ser Gly Val	Asp Val I 1350 Tyr Arg M 1365 Lys Gly F Asp Asp I Pro Gly I His Ala F 1430 Arg His F 1445 Gly Ser T Leu Arg S Arg Ala F Gly Pro F 1510 Gly Ile F	Lys His Met Gln Pro Val Leu Gly 1400 Lys Thr 1415 Ala Lys Pro Glu Thr Gln Ser Arg 1480 His Gln 1495 Pro Tyr Pro Asp	Ser Ile 1370 Met Ser 1385 Gly Ile Gly Leu Ala Ile Ala Glu 1450 Pro Glu 1465 Lys Leu Glu Ala Pro Gln Thr Ser 1530 Ser Gly	Thr Ser 1355 Arg Arg Gln Tyr Tyr Val Leu Ser 1420 Ser Pro 1435 Met Asp Lys Pro Pro Asp Ser His 1500 Gly Ala 1515 Glu Pro	Trp Glu Asp Ile 1405 Val Glu Arg Ser Met 1485 Arg Gly Val	Asn 1390 His Ala Gly Ala Leu 1470 Gly Gln Gln Ser Leu	Arg 1375 Met Leu Glu Glu His 1455 Pro Cys Phe Leu Tyr 1535 Arg	1360 Ala Thr Arg Gly Asp 1440 His Gln Ser Cys Asp 1520 His
Arg Gln Lys Val  Arg Gln Lys Val  1380 Pro Ala Val Gln  1395 Ser Lys Ser Asp  1410 Lys Glu Ser Arg  1425 Arg Phe Tyr Arg  His Gly Gly His G  1460 Lys Gln Ser Ser  1475 Leu Pro Glu His 1  1490 Glu Ser Lys Asn G  1505 Tyr Gly Ser Lys G  Asn Ser Gly Val  1540	Asp Val I 1350 Tyr Arg M 1365 Lys Gly F Asp Asp I Pro Gly I His Ala F 1430 Arg His F 1445 Gly Ser I Call Arg S Arg Ala F 1510 Gly Ile F 1525 Lys Tyr F	Lys His Met Gln Pro Val Leu Gly 1400 Lys Thr 1415 Ala Lys Pro Glu Thr Gln Ser Arg 1480 His Gln 1495 Pro Tyr Pro Asp Ala Ala	Ser Ile 1370 Met Ser 1385 Gly Ile Gly Leu Ala Ile Ala Glu 1450 Pro Glu 1465 Lys Leu Glu Ala Pro Gln Thr Ser 1530 Ser Gly 1545	Thr Ser 1355 Arg Arg Gln Tyr Tyr Val Leu Ser 1420 Ser Pro 1435 Met Asp Lys Pro Pro Asp Ser His 1500 Gly Ala 1515 Glu Pro Gln Glu	Trp Glu Asp Ile 1405 Val Glu Arg Ser Met 1485 Arg Gly Val Ser	Ser Asn 1390 His Ala Gly Ala Leu 1470 Gly Gln Gln Ser Leu 1550	Arg 1375 Met Leu Glu Glu His 1455 Pro Cys Phe Leu Tyr 1535 Arg	1360 Ala Thr Arg Gly Asp 1440 His Gln Ser Cys Asp 1520 His Leu
Arg Gln Lys Val  Arg Gln Lys Val  1380 Pro Ala Val Gln  1395 Ser Lys Ser Asp  1410 Lys Glu Ser Arg  1425 Arg Phe Tyr Arg  His Gly Gly His G  1460 Lys Gln Ser Ser  1475 Leu Pro Glu His 1490 Glu Ser Lys Asn G  1505 Tyr Gly Ser Lys Glu  Asn Ser Gly Val  1540 Asn His Lys Glu	Asp Val I 1350 Tyr Arg M 1365 Lys Gly F Asp Asp I Pro Gly I His Ala F 1430 Arg His F 1445 Gly Ser I Call Arg S Arg Ala F 1510 Gly Ile F 1525 Lys Tyr F	Lys His  Met Gln  Pro Val  Leu Gly 1400  Lys Thr  1415  Ala Lys  Pro Glu  Thr Gln  Ser Arg 1480  His Gln  1495  Pro Tyr  Pro Asp  Ala Ala  Leu Ser	Ser Ile 1370 Met Ser 1385 Gly Ile Gly Leu Ala Ile Ala Glu 1450 Pro Glu 1465 Lys Leu Glu Ala Pro Gln Thr Ser 1530 Ser Gly 1545 Lys Glu	Thr Ser 1355 Arg Arg Gln Tyr Tyr Val Leu Ser 1420 Ser Pro 1435 Met Asp Lys Pro Pro Asp Ser His 1500 Gly Ala 1515 Glu Pro Gln Glu	Trp Glu Asp Ile 1405 Val Glu Arg Ser Met 1485 Arg Gly Val Ser Arg	Ser Asn 1390 His Ala Gly Ala Leu 1470 Gly Gln Gln Ser Leu 1550 Pro	Arg 1375 Met Leu Glu Glu His 1455 Pro Cys Phe Leu Tyr 1535 Arg	1360 Ala Thr Arg Gly Asp 1440 His Gln Ser Cys Asp 1520 His Leu
Arg Gln Lys Val  Arg Gln Lys Val  1380 Pro Ala Val Gln  1395 Ser Lys Ser Asp  1410 Lys Glu Ser Arg  1425 Arg Phe Tyr Arg  His Gly Gly His G  1460 Lys Gln Ser Ser  1475 Leu Pro Glu His 1  1490 Glu Ser Lys Asn G  1505 Tyr Gly Ser Lys G  Asn Ser Gly Val  1540	Asp Val I 1350 Tyr Arg M 1365 Lys Gly F Asp Asp I Pro Gly I His Ala F 1430 Arg His F 1445 Gly Ser I Leu Arg S Arg Ala F Gly Pro F 1510 Gly Ile F 1525 Lys Tyr F	Lys His  Met Gln  Pro Val  Leu Gly 1400  Lys Thr  1415  Ala Lys  Pro Glu  Thr Gln  Ser Arg 1480  His Gln  1495  Pro Tyr  Pro Asp  Ala Ala  Leu Ser 1560	Ser Ile 1370 Met Ser 1385 Gly Ile Gly Leu Ala Ile Ala Glu 1450 Pro Glu 1465 Lys Leu Glu Ala Pro Gln Thr Ser 1530 Ser Gly 1545 Lys Glu	Thr Ser 1355 Arg Arg Gln Tyr Tyr Val Leu Ser 1420 Ser Pro 1435 Met Asp Lys Pro Pro Asp Ser His 1500 Gly Ala 1515 Glu Pro Gln Glu Met Glu	Trp Glu Asp Ile 1405 Val Glu Arg Ser Met 1485 Arg Gly Val Ser Arg 1565	Ser Asn 1390 His Ala Gly Ala Leu 1470 Gly Gln Gln Ser Leu 1550 Pro	Arg 1375 Met Leu Glu Glu His 1455 Pro Cys Phe Leu Tyr 1535 Arg	1360 Ala Thr Arg Gly Asp 1440 His Gln Ser Cys Asp 1520 His Leu Val

1570 1575 1580 Glu Glu His Leu Thr Gln Ser Ile Val Pro Pro Pro Lys Pro Glu Arg 1590 1595 1600 Ser His Ser Leu Lys Leu His His Thr Gln Asn Val Glu Arg Asp Pro 1610 1615 1605 Ser Val Leu Tyr Gln Tyr Gln Pro His Gly Lys Arg Gln Ser Ser Val 1620 1625 Thr Val Val Ser Gln Tyr Asp Asn Leu Glu Asp Tyr His Ser Leu Pro 1635 1640 Gln His Gln Arg Gly Val Phe Gly Gly Gly Met Gly Thr Tyr Val 1650 1655 1660 Pro Pro Gly Phe Pro His Pro Gln Ser Arg Thr Tyr Ala Thr Ala Leu 1675 1665 1670 Gly Gln Gly Ala Phe Leu Pro Ala Glu Leu Ser Leu Gln His Pro Glu 1685 1690 Thr Gln Ile His Ala Glu 1700 <210> 435 <211> 160 <212> PRT <213> Homo sapiens

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<211> 396

<212> PRT

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Asp Met Phe Thr His Gly Ile Gln Ser Ala Ala His Phe Val Met Phe

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Asp Leu Gly Asp Lys Tyr Asn Ser Met Glu Asp Ala Lys Val Tyr Val
                    70
Ala Lys Val Asp Cys Thr Ala His Ser Asp Val Cys Ser Ala Gln Gly
                                    90
Val Arg Gly Tyr Pro Thr Leu Lys Leu Phe Lys Pro Gly Gln Glu Ala
                              105
Val Lys Tyr Gln Gly Pro Arg Asp Phe Gln Thr Leu Glu Asn Trp Met
                          120
Leu Gln Thr Leu Asn Glu Glu Pro Val Thr Pro Glu Pro Glu Val Glu
                      135
                                           140
Pro Pro Ser Ala Pro Glu Leu Lys Gln Gly Leu Tyr Glu Leu Ser Ala
                   150
                                       155
Ser Asn Phe Glu Leu His Val Ala Gln Gly Asp His Phe Ile Lys Phe
                                   170
Phe Ala Pro Trp Cys Gly His Cys Lys Ala Leu Ala Pro Thr Trp Glu
           180
                               185
Gln Leu Ala Leu Gly Leu Glu His Ser Glu Thr Val Lys Ile Gly Lys
                           200
Val Asp Cys Thr Gln His Tyr Glu Leu Cys Ser Gly Asn Gln Val Arg
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Gly Tyr Pro Thr Leu Leu Trp Phe Arg Asp Gly Lys Lys Val Asp Gln
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Tyr Lys Gly Lys Arg Asp Leu Glu Ser Leu Arg Glu Tyr Val Glu Ser
                                   250
Gln Leu Gln Arg Thr Glu Thr Gly Ala Thr Glu Thr Val Thr Pro Ser
           260
                               265
Glu Ala Pro Val Leu Ala Ala Glu Pro Glu Ala Asp Lys Gly Thr Val
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Leu Ala Leu Thr Glu Asn Thr Phe Asp Asp Thr Ile Ala Glu Gly Ile
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                                           300
Thr Phe Ile Lys Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Thr Leu
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                                       315
Ala Pro Thr Trp Glu Glu Leu Ser Lys Lys Glu Phe Pro Gly Leu Ala
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               325
Gly Val Lys Ile Ala Glu Val Asp Cys Thr Ala Glu Arg Asn Ile Cys
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                               345
Ser Lys Tyr Ser Val Arg Gly Tyr Pro Thr Leu Leu Leu Phe Arg Gly
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<212> PRT

<213> Homo sapiens

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<213> Homo sapiens

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Pro Ser Ile Met Lys Ser Leu Met Asp His Thr Ile Pro Glu Val

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<sup>&</sup>lt;211> 378

<sup>&</sup>lt;212> PRT

<213> Homo sapiens

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<sup>&</sup>lt;211> 2239

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<sup>&</sup>lt;213> Homo sapiens

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<211> 337
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<213> Homo sapiens
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tcaggaaagc ctgttgtgtc caccatctcc aaaggaggtt acctgcaggg aaatgttaac 240
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<210> 443
<211> 739
<212> DNA
<213> Homo sapiens
<400> 443
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atatteegte eteaaaaagt actgagttae etgtggaetg gagtattaaa aegegaetee 180
ttttcacctc ttctcaaccc tttacctggg cagatcattt gaaagcacag gaagaagctc 240
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aaggtettgt ceageattgt agggeaacag aagttaettt geetaaaagt atacaggate 300

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ccaaactete etetgagete egttgtacet tecageagag cettatetat tggetecace 360
ctgctttgtc ttggctacca ctgttccctc gtattggagc tgatagaaaa atggctggaa 420
agacaagtcc ttggtcaaat gatgcaaccc tgcagcatgt tttaatgagt gactggtctg 480
tgagctttac ttctctatat aatttgctga agacaaaact ttgcccctat ttctacgttt 540
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cagctctcat atctccaaca actcgaggtt taagagaagc tatgagaaat gaaggtattq 660
aattttetet geetttaata aaagaaagtg geeataagaa ggagacagea tetggaacaa 720
gcttgggata tggggagga
                                                                  739
<210> 444
<211> 738
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(738)
<223> n = A, T, C or G
<400> 444
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tgataaatac agtttgttat tgnggtctca ttaaattaat cagctttttc acactggggt 120
aaagaaacag atgatgatac tagggaatgg aaacaaaatt ggaaacctgg gttatttggg 180
gatttatatt gtactctgca cagttgccct ttttttttagg cgtgttccct ggaaaagagg 240
gacggatgaa cctggaagta agtaaaagac attctaggtg tgtagcatca aggcagttaa 300
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gaacttaatg totagtcaca cgtcattggc atgttttctc cccagcattt aattacaaag 480
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gccgttttga tganaaaaat gggtttggtg ttcaggatct ccaattataa atgtagtctc 600
teageaceae atteegtaaa gatgatttee eaagtaaegg tatttgaeta agttgeteea 660
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<211> 716
<212> DNA
<213> Homo sapiens
<400> 445
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teggeeegga aggettette ettggeaaga tgggatteeg ggaggeggtg geggeeggag 180
acgtggattt gcctcaggtg cggagccgca gctacaggag gatgctcgcg aggaccccca 240
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cgtgctccca ggtggacaga cgccttcgtg ggcctgagca cttgcgqccq qcacatqtcc 540
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ctgacagccg agetgatggc gcaccccggc taccccagtg tgcctcccac cggcggctgc 660
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<210> 446
<211> 641
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (1)...(641)
<223> n = A, T, C or G
<400> 446
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eegaggneeg eeeegtgggt eeggeeegee gtggegeete ategetgete ggeeeggaag 120
gettntteet tggcaagatg ggatteeggg aggeggngge ggeeggagae gtggatttge 180
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gagggtactg tgaggccgtt aggagctggc ggnggatgac ttccgcattc aaacactgga 300
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tetntegete geeetetagg ngegggagga getegaggee caactaanet getteeggga 420
getgetggge agggeeceea egeaegegga egggeaeeag eaegtgeaeg tgeteeeagg 480
nggacagacg cettegtggg cetganeact tgeggeeggn acatgtteec teaceegegg 540
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ctgatggccc accceggcta ccccangtgt gcctccaccc g
<210> 447
<211> 652
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(652)
<223> n = A,T,C or G
<400> 447
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ttcgccaaag gaaatagcaa agtttatctt ctgtacaaga acactaaatt ggaaaaaact 180
gagaatctat cttgatgaaa ggagagatgt cttggatgac cttgtaacat tgcataattt 240
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agagogtgga gagtatottg aaactottat aacaaagtto toacatagat totgtgottg 360
caaccetgat ttaatgegag aacttggeet tagteetgat getgtetatg taetgtgeta 420
ctctttgatt ctactttcca ttgacctcac tagccctcat gtgaagaata aaatgtcaaa 480
aagggaattt attegaaata eeeegegege tgeteaaaat attagtgaag aattttgtan 540
ggcatcttta tgacaatatc tacccttatt gggccatggn ggctggcata aaaaagcacc 600
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<211> 677
<212> DNA
<213> Homo sapiens
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cagaacttca ttgaccccct ccagaacctg tgcgagaaag acctgaagga gatccagcac 120
cacctgaaga aactggaggg ccgccgcctg gactttgact acaagaagaa gcggcagggc 180
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gcagaaacca gcatgcacaa cctcctggag actgacatcg agcaggtgag tcagctctcg 300
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ccgaagcccc gggagccctt tgaccttgga gagcctgagc agtccaacgg gggcttcccc 480
tgcaccacag cccccaagat cgcagcttca tcgtctttcc gatcttccga caagcccatc 540
cggaccecta gccggagcat gccgccctg gaccagccga gctgcaaggc gctgtacgac 600
ttcgagcccg agaacgacgg ggagctgggc ttcatgaggg cgacgtcatc acgctgacca 660
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accagatcga tgagaac
                                                                   677
<210> 449
<211> 603
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(603)
<223> n = A, T, C or G
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ttgccctgga ccgtgcccaa agctgtgtgc tcatctctgc gcccctcatg tacttctgac 120
qaqqqqqtq caqqqq caqaqcaqaq cctqqqqtcc qqaqqcttca ctqqaccaca 180
gggggagggg aatgtgaatg tggcctggcc canagaactc cccatttcat cgattttqca 240
ttgggcgata gaggaagcag atgtcggggc tgcctgcctt ggtctanagg agatggctgg 300
ggccacttcc cacagggtga agtggcagcg gctcagcaag gggagcctgg ccaccagggg 360
ctgggacatg cgctcactgg aacctttgtg cttggccctc ggcagcgcgg ctgtggtccc 420
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cacaggeete eetgggttgg gatgggggea agttaaaaag etgaaaaggt aettggettt 540
ctgagggcgg gcttgggagc aggccctgca gganaccatg ttctctgtcc tcagcagatc 600
cac
                                                                   603
<210> 450
<211> 678
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(678)
<223> n = A, T, C or G
<400> 450
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gaaggetgee tacaetggge aetgttttag atteteatat eatttaaaca geaaggaggt 180
tcagggaaga ataaccgtag ccttgggtaa tccactaggg cttttgtgag taggagagct 240
gatacctcac attcttagca ggtgaaaact tgccatgatg gaaacagata gtgaagagtt 300
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ctgagttcat aagtaattct agtgaacctt agtaggaatt ctgggtaaga aaatgaggtt 420
gccattggtc ttgtttgcat caccaagacc agacatccag aagagcccct caccttgaaa 480
agcagacaga ttttaaatta acceeteet teecaeteae etteatetee etaagagttt 540
tggccattta attccacatt ttgaaaggaa tacattggtg aaatttggga agagaatctg 600
tgctatgcaa tgtttcatta aaatcttcag tttttcaagt ctctctaaaa ataatttgta 660
gatctatctt ggatggat
<210> 451
<211> 651
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(651)
<223> n = A,T,C or G
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<400> 451
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aaaccaagat tctgtacaat attctaacat tatatgtaca taaaattata ttactcataa 120
ctatattgaa aagtettatt tgtagaatat ggetggeaae aaagaaagae eeataceatt 180
tagcgtttga agcagggcag gtagcaagag aacattagca aagacacctt tgtgcctgga 240
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tegttgttte acattetagt agggaattet geageaggeg atgegaaaaa naanacatgg 360
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aatccaagtt gcattggaag ttcactcatt ctccattcat tatgcatgcc tccagtgatt 480
taatgaattt cagcaggngg aaaagacagc tttgaacaga tcagatgggc tgtgagtcan 540
attettgatt ettttteete atttggetee tgaatgttge anaaaactgg ttttgtacae 600
tggggaagga gagagtgaag accetecagt tggtteetea gteageteeg t
<210> 452
<211> 679
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(679)
<223> n = A, T, C or G
<400> 452
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gtgtatgaaa tcagcctgtc acccacaggt gtatctaggg tctgtttgta tcctggcttt 240
gttgacgtga aagaagctga ctggatattg gaacagcttt gtcaagatgt tccctggaaa 300
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tcactaggga ggtgccccat tattgcttca ctaagttttg gtgccacacg cacatttgag 600
atgagaaaga agccaccacc agaagagaat ggagactaca catatgtgga aagagtgaag 660
atacccttgg atcatggta
                                                                   679
<210> 453
<211> 630
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(630)
<223> n = A, T, C \text{ or } G
<400> 453
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gaagaagcag gaggctaaga aagtggtgaa tcccctgttt gagaaaaggc ctaagaattt 120
tggcattgga caggacatcc agcccaaaag agacctcacc cgctttgtga aatggccccg 180
ctatatcagg ttgcagcggc agagagccat cctctataag cggctgaaag tgcctcctgc 240
gattaaccag ttcacccagg ccctggaccg ccaaacagct actcagctgc ttaagctggc 300
ccacaagtac agaccagaga caaagcaaga gaagaagcag agactgttgg cccgggccga 360
gaagaagget getggeaaag gggaegteee aacgaagaga ceacetgtee ttegageagg 420
agttaacacc cgtcaccacc ttggtggaga acaagaaagc tcagctggtg gtgattgcac 480
acgacgtgga teccategag etggttgtet tettgeetge eetgtgtegt aaaatggggg 540
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teeettaetg cattateaag ggaaaggeaa gaetgggaeg tetagteeac aggaagaeet 600
gcaccactgt cgccttccac aggtgaactc
<210> 454
<211> 677
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(677)
\langle 223 \rangle n = A, T, C or G
<400> 454
gaattcgaac cccttcgccc gcatgcggna catccccttg gccccagggt cagactggcg 60
cgatctgccc aacatcgagg tgcggctctc agacggcacc atggccagga agctgcggta 120
tacccaccat gacaggaaga acggccgcag cagctctggg gccctccgtg gggtctgctc 180
ctgcgtggaa gccggcaaag cctgcgaccc cgcagccagg cagttcaaca ccctcatccc 240
ctggtgcctg ccccacaccg ggaaccggca caaccactgg gctggcctct atggaaggct 300
cgagtgggac ggcttcttca gcacaaccgt caccaacccc gagcccatgg gcaagcaggg 360
eegegtgete cacceagage ageacegtgt ggtgagegtg egggagtgtg ceegeteeca 420
gggetteeet gacacetace ggetettegg caacateetg gacaageace ggeaggtggg 480
caatgoogtg ccaccgcccc tggcaaagcc attggcttgg agatcaagct ttgtattgtt 540
ggccaaagcc cgagagagtg cctcagctaa aataaaggag gaggaagctg ctaaggacta 600
gttctgcctt cccgtcaccc ctgtttctgg caccaggaat cccccacaat gcacttgatg 660
gtggggtttt aacatgt
                                                                   677
<210> 455
<211> 598
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(598)
<223> n = A, T, C or G
<400> 455
ttttttggtt tataggagag atttatttga agaaatatta caacatataa aaactacata 60
aagtettaat tteeaeteat aeagtggtag atttgatata atgeataata aaaaaetttt 120
aaaatccaga atgcacaaag tactgcacaa tttgatcact aaatcattag ttgataagcg 180
aacctcacac aacagettea tgteageeaa ggeeacaaae accatgtace acacatgtga 240
acggacagat tgacatgtta aaaacacaac atcagtgcat gttggggatt cctggtgcca 300
gaaacagggg tgacgggagg gcagaactag tccttagcag cttcctcctc ctttatttta 360
gctgaggcac tctctcgggc tttggccaac atacaaagct tgatctccaa gccaatggct 420
ttggccaggg gcggtggcac ggcattgecc acctgccggt gcttngtcca ggatgttgcc 480
cgaagageeg gtaggtggte aagggaagee eetggggaag egggeaeaet eeeggaeget 540
naccacagg tgctgntttt gggtggagca ccgcggcctt gcttgcccat gggctcgg
<210> 456
<211> 574
<212> DNA
<213> Homo sapiens
<400> 456
ggaattegaa eeeetteggg geggggagee eegtagaace gagggggteg geeegggggt 60
cccgggggag gtggagatgg tgaaggggca gccgttcgac gtgggcccgc gctacacgca 120
gttgcagtac atcggcgagg gcgcgtacgg catggtcagc tcggcctatg accacgtgcg 180
```

```
caagactogo gtggccatca agaagatcag cocottogaa catcagacot actgocagog 240
cacgeteegg gagateeaga teetgetgeg etteegeeat gagaatgtea teggeateeg 300
agacattetg egggegteea ceetggaage catgagagat gtetacattg tgeaggacet 360
gatggagact gacctgtaca agttgctgaa aagccagcag ctgagcaatg accatatctg 420
ctacttecte taccagatee tgeggggeet caagtacate caeteegeea aegtgeteea 480
ccgagatcta aagccctcca acctgcttca tcaacaccac ctggcgacct ttaaaatttg 540
tgaatttccg gcctggcccc cggattgccc gaat
<210> 457
<211> 546
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(546)
<223> n = A, T, C or G
<400> 457
ttttttgaca catctctata tttatatatt agacgggtca gggaggtggc aggggcgccg 60
ggctctccac gcccccagc tccacttctg ctcaccacac acagaagcag cgagggcacg 120
cgaagtgaca getttgacag ggaggggatt cggcccggcc tggctcctca gggatgctag 180
cccttgagac taaggaatgt tccttcaggg aaactagggt ggggtttgaa tganatgagg 240
ggggcaggca tggccctgag tccctactca gcgcccccca ccctccacct ctgcccttca 300
gcaggttggg gcagccagaa cccttccatt ccagaactgc cagagactgg gacgctgggg 360
aaggtaaggg cgcagcagca gcagcgggag attgaactgg ggccacctga gctcccgagg 420
ccccgtgggg agggcgggtg gggaggaaaa ggccttggcc tgcctgaagc tggaggcctc 480
agcaaaggag agaggtggcc aggcccatgc tccaccccgg cctgggctgc caanggtccc 540
gggctg
<210> 458
<211> 674
<212> DNA
<213> Homo sapiens
<400> 458
qaattcqaac cccttcqqta ttattaaqaa ctaaqaqaat aqcttqccaq atacaaatqq 60
aaacaccttc caaatgagtc ggagaaaatg tcttgcagta ttatgggtaa aatagcaaag 120
agcttgggaa tacagtttgc taatatcaag tccttaacaa cgaccattct tcattcaaga 180
ttagttgtgt ataaatacat gcttcttcag gagttgactt agaaaacaag caaacaaaca 240
aacatcagaa actatttaca actgggagca atccttgaag aacataaaga atataaatat 300
caacaaaggc tgaaaactct tttttagatt aaagatcaaa tggacatgtc atcggaatgt 360
attqtatqqc tcttqattaa atcctqqaqc aaaqtqqaqa qtqaqqaaca actqtaaaqa 420
atgtgaatac ggactgtgta ttagataaca gtaccataaa tttcctggat gggataatta 480
tgttgtgact atgtaagaga atattttgcc cttagaagat atatgatgaa gcatttagaa 540
gtaaagtatc atgacatctt gcaaataact ttcaagtgat tcagccagat atataaaaat 600
tatatataac acattatata atttatattt atataattat aatacattat ataatttata 660
cattataatt atat
                                                                   674
<210> 459
<211> 682
<212> DNA
<213> Homo sapiens
<400> 459
tttttttaaa tooatggott gttaattgto atoocagtta tttacatgtg actatagaga 60
ctgcattctc ccagctgcca ggccgccagg gctttgccac tggtataatt tataacacga 120
ctaattaaaa tgaatttgct tgcaataagg ttctgtgtgc tatttgtggg agaggagtta 180
```

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ttaaaaatttt cagtacagta atagtaaact tgaatgcaaa gtaataataa tcatacattt 240
ttaattacat gtttaatacc catttggcta atgtagaact attctgaaaa ttacttggga 300
tcagcacaat gtctttttgt gcttagtagt atccaaagac atccttctga atgggcttag 360
caatatgcac tgtcatcaag atacagctgt ttgatgacag acacacagtg tgttcctatg 420
atactttgca caagatcagc tatgacaaat acaagttcat tttgcttatt gcaggcaaat 480
aatgteettt geaggaactt ggatggagee agaggeeatt attetaagtg aaatacetea 540
ggagtggaaa accaaatacc atatgttctc acttacaagt gggaactaag ctatgggtac 600
acaaacqcat ataqaqtaat qqactctqqc qactcatact acatattqaq tacaatqtac 660
actacttggg tgatgggtgc ac
<210> 460
<211> 663
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(663)
<223> n = A, T, C or G
<400> 460
gaattegaae eeettegegg ggegegegag eggegeeage teggggeage ggaaeceaga 60
qaaqctqaqq qqqcqqtaqc qqcqqcqacq qcqacqacqa cqactcccqc qcqtqtqccc 120
agectettee egeogeagee gecettttee teecteeett aegteeeega gtgeggeagt 180
accgcctcct tcccagccgc gcggcttcct ccagacctct cggcgcgggt gagccctatt 240
cccagaggca ggtggtgctg accctgtaac ccaaaggagg aaacagctgg ctaagctcat 300
cattgttact ggtgggcacc' atgtccttga agcttcaggc aagcaatgta accaacaaga 360
atgaccccaa gtccatcaac tctcgagtct tcattggaaa cctcaacaca gctctggtga 420
agaaatcaga tgtggagacc atcttctcta agtatggccg tgtggccggc tgttctgtgc 480
acaagggeta tgeetttgtt cagtaeteea atgagegeea tgeeegggea getgtgetgg 540
gagagaatgg gcgggtgctg gccgggcaga ccctggacat caacatggct ggagagccta 600
agcetgacag acceaagggg ctaaaganaa geagcatetg geatatacag getettegae 660
tac
                                                                   663
<210> 461
<211> 612
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(612)
\langle 223 \rangle n = A, T, C or G
<400> 461
ttttttggga tccaatctnt ttattgtcag ggtcccctcc ctgnggcccc ccgccaaacc 60
tatagaaaaa acccaagcet gggagtgtee tggggagggg aggtagtatg gggaaaccce 120
tgtgctctac cctntggcct gggcagtgca nacagggagg gctcatgggg aaggagtagg 180
ccagtaactc cacctgcana ggacatggca ctggctggga tgcgttgggg gaggaggcgc 240
ctgctgccag ctttcctntg gtacccgctg gggggtggca tccagggttg ggtgcccggc 300
ttgaggcctg gggcagcgat gcccttcacc tgctggnggc cattgctcct gtcaggctgc 360
ttactgcaag gccccatcat ccgcgtctgt gtcctggctg tgttccagct cttcctcgct 420
gngtgtcagg agccettect categeegte gtetegggte eqtgetteee eetggggcag 480
geetgeetea naagttgtgt tetettgggg ggetggtgge eggttgttge caeegeaeeg 540
caccaccact ggcaccggca ccgntgcacc accaccgccg ccgccgccgn tggngccacc 600
ttcatcaccc tt
                                                                   612
```

```
<211> 672
<212> DNA
<213> Homo sapiens
<400> 462
gaattcgaac cccttcggat ggaagggcc ggggcagcgt cggggaaagg aagggccgga 60
ggcgcggcgg cgggcggccg agaggggcgg cggcggcggc ggcggcgggg ttcccqcqcc 120
gcggagcccg gcccgagagc cgcgtccacg ttcctgcctc ctgctcccgc cgccctgggg 180
egecgecatg aegecegate tgeteaactt eagececaga tgteaceaag eteteggaet 240
ctaacaagga gaacgcgctg cacagctaca gcacccagaa gggccccctg aaggcagggg 300
agcagcgggc gggctctgag gtcatcagcc ggggtggccc tcggaaggcg gacgggcagc 360
gtcaggcett ggactacgtg gagetetege egetgaeeca ggetteeeeg cagegggeee 420
gcaccccage eegcacteet gacegeeetg gecaageagg aggagetgga gegggaeetg 480
gcccagcgct ccgaggagcg gcgcaagtgg tttgaggcca cagacagcag gaccccagag 540
gtgcctgctg gtgaggggcc gcgccggggc ctgggtgccc cctgactgag gaccagcaaa 600
accggcttag tgaggagatc gagaagaagt ggcaggagct ggagaagctt gcccttgcgg 660
gagaataacc gg
<210> 463
<211> 562
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(562)
<223> n = A, T, C or G
<400> 463
ttttttaaag tataaagtgt tttggaaaaa aaggaaaaan ntctatataa aaatctcttc 60
acatataaaa teetgaagaa ggtgeaaggt gagaceeagt gegaggggeg tgeteagata 120
tgcagtgtgt gtgtgtgtg gtgtgtgtgt gtatccgtgt gtacatgtgt gcacgtgtgt 180
agtgcacgtg tggcccacag agggtgggga gaaagcttgg ctttttactt ccatccagga 300
gggaaggagg geggetggte etceageetg gagggtetge agetgggegg gaeetetaet 360
cagecagget gttgegeate gaeteettet eetggaggge ggeeatggea agaegeaggt 420
gctccttcag ctgctcgatc tcccgctcag accgtgtctt gatgtggctc aactccacat 480
agacgtcctg gtactttccc naggtgaagc gcttgtcctt ctgcatcatc tggagctcgt 540
cccggaggca ctgcaccttc ct
                                                                 562
<210> 464
<211> 553
<212> DNA
<213> Homo sapiens
<400> 464
gaattcgaac cccttcggga ccaggaaccc aggagagcat ggccacgctg cgccggcttc 60
gggaggegee geggeactta etggtttgeg agaaateeaa etteggeaae caeaagtege 120
gccaccggca tcttgtgcag acgcactact ataactacag ggtttcattt ctcattcctq 180
aatgtgggat actatcggaa gaactgaaaa acctggtcat gaacactgga ccctattact 240
ttgtgaagaa tttacctctt catgaattaa ttacacctga attcatcagt acctttataa 300
agaaaggttc ttgctatgca ctaacataca atacacatat tgatgaagat aatactgttg 360
ccctgctacc aaatgggaaa ttaattttgt cactggataa agacacttat gaagaaactg 420
gacttcaggg tcatccatct cagttttctg gcagaaaaat tatgaaattt agttcagaag 480
aatcgacaat gatgtcatat ttttccaagt accaaattca ggagcatcag ccaaaagtag 540
cactgagccc gtt
                                                                 553
```

203

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<211> 383
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(383)
<223> n = A,T,C or G
<400> 465
tttttggaag aaaacacgat ttttaatttt tattttttat gggggacagn gatcatttgc 60
cccaacagcc atntgaagcc aatagtcctg attattaaaa atcacaaagt tatataaatg 120
ntctcctcct tttcgaaaac catgttcatt tttttcccaa naaacagggc tgtctgcaaa 180
gccttgaacg gacagngtaa cccatggagc taacttcggt tcatcaaagt agngacagan 240
atgttccaat agganacaga tcttntntgg aagtatgaag ccagngattg tacacaaata 300
agettttgcc accactgtgc ttggctcagg acagcaatag gttgatatga aattattagg 360
ctcattattt aggncgacat tac
<210> 466
<211> 673
<212> DNA
<213> Homo sapiens
<400> 466
gaattcgaac cccttcgctc cctcctgcac gcaatggtgg cctatgatcc cgatgagaga 60
atcgccgccc accaggccct gcagcacccc tacttccaag aacagaggaa aacagagaag 120
egggetetgg geageeacag aaaagetgge ttteeggage accetgtgge aceggaacea 180
ctcagtaaca gctgccagat ttccaaggag ggcagaaagc agaaacagtc cctaaagcaa 240
gaggaggacc gtcccaagag acgaggaccg gcctatgtca tggaactgcc caaactaaag 300
ctttcgggag tggtcagact gtcgtcttac tccagcccca cgctgcagtc cgtqcttqqa 360
tctggaacaa atggaagagt gccggtgctg agacccttga agtgcatccc tgcgagcaag 420
aaggtagege ggaaceaget tetetgaegg egetgetett egaeceagee eaggeegeea 480
ctgaattttg tgtctgtaat ttttctttga cagacagatc cgcagaagga ccttaagcct 540
gccccgcagc agtgtcgcct gcccaccata gtgcggaaag gcggaagata actgagcagc 600
accgtcgtct cgacttcgga ggcaacacca agcccgaccg ggccaggcct gggtgatctg 660
ctgctgagac gcc
                                                                   673
<210> 467
<211> 373
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(373)
<223> n = A, T, C or G
<400> 467
tttttactgg aacgacagct tattntttaa taaaagtcag gggngtcagc agngtcactg 60
gtaanacatg atggcgctcc acgactgacc agcagcgctg qgaagqqaca cgcanaaccc 120
accttccaac cacgcccaac acatnacana aatgcctgct cgtttgtttt gattcatata 180
caaagttaca aagtatttcc tgccccaaat tnttaacgaa aatgaaagaa aaccctanaa 240
tgcgggggtt ttacaagtat attagcccan aacatcctag qcagctgcnc gggccgcggg 300
tgcggcaggg cgcagggcaa cacccaaagc cccggccagc gcgaaacgga cgcaggcgca 360
tccccagccc tcc
                                                                   373
<210> 468
```

<210> 468 <211> 573

```
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(573)
<223> n = A, T, C \text{ or } G
<400> 468
gaattegaac ceettegetg etgteetact tgatgettgt caetgteatg atgtggeece 60
tngctgtgta ccaccgactg tgggatcgag catatgtgcg gctgaagcca gctctgcagc 120
ggctagactt cagtgtccgt ggctacatga tgtccaagca gagagagaga caattacgcc 180
geagagetet ceaeceagaa egageeatgg acaaceacag tgacagegaa gaggagettg 240
etgeettetg teeteagetg gaegatteta etgttgeeag ggaattggee ateaeagaet 300
ctgagcactc agacgctgaa gtctcctgta cagacaatgg cacattcaat ctttcaaggg 360
gccaaacacc tctaacggaa ggctctgaag acctagatgg tcacagtgat ccagaggaat 420
cetttqccaq agacettcca qaettccett ccattaatat qqatectqct qqcetqqatq 480
atgangacga cactagcatt ggcatgccca gcttgatgta ccgttctccg ccagggggct 540
gaggageeee aaggeeeeae etgeeageee ggg
                                                                   573
<210> 469
<211> 635
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(635)
<223> n = A, T, C or G
<400> 469
tenegateta gaactaggtt ggacaggett geteaagttt caccagagtt antactggec 60
tetgttegea gagtttttag ttnnacactg cagaattgge agactacacg gtttatggaa 120
gttgaagtag caataagatt gctgtatatg ttggcagaag ctcttccagt atctcatggt 180
geteacttet caggtgatgt tteaaaaget agtgetttge aggatatgat gegaactgta 240
agtatactgg agataatttt gaccataaat ttctgttttc agtataagct aatgggagtt 300
ccttaattgt tagagcttag tatatgttaa taccggggca ttttgatgtt gcaataaata 360
agaagaggtt teetaacttt tteetgatet agetggtaae ateaggagte agtteetate 420
agcatacatc tgtgacattg gagttcttcg aaactgttgt tagatatgaa aagtttttca 480
cagttgaacc tcagcacatt ccatgtgtac taatggettt cttagatcac agaggtctgc 540
ggcattccag ngcaaaagtt cggagcagga cggcttacct gttttctaga tttgtcaaat 600
ctctcaataa gcaaatgaat cctttccttg aggat
                                                                   635
<210> 470
<211> 593
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(593)
<223> n = A, T, C or G
<400> 470
gaattegaae eetteggtat taacaaatat ntacatttet atttttataa teeataagga 60
tatgcctgtt ttaaataaca tacatattaa caatatctat caggaaaacc ctcaagacag 120
cttctagtta aaaccttngn tgctgtcctc tcaaactata tttataaaaa tttgctaggg 180
ccaaatccat acttgcagaa taattcatca aattttattt ttaagngaaa agtaaccttt 240
```

```
caggicattic agcagicatac attgacaatic taggigtatat atgitatigtat gitticitatt 300
gtatgtctat atatgtatgt ggggaggaca ggagtgaatg ttcacacact tttcttgcgt 360
actcaactaa attggagaat gtttctgaag aaaattggat gaaattagct gctgagattg 420
agtttctgcc ttaaaatctg aaacaaaaaa agggacaaat tgctggtang atctactgac 480
tgtngccatc accagaacac ttagtttctt cccagacatg aatttcctga caggctctga 540
gccagaaaca cactgtgggc gtgcatntgg gtcaccctgg atatgcctcc act
<210> 471
<211> 581
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(581)
\langle 223 \rangle n = A,T,C or G
<400> 471
tttttttaat cangggacat ttattaacat gcttcaaaag tgaccaaagt gtccagccag 60
cacaatagcc gaggcaatca acgttctctt agtgtgtgat ctcgtccaaa acaccaaata 120
aataggttta ggaataacct caaataaatt gtaatttaac ttcgcccaaa attatacatc 180
ctctactgct cttccctgct cctgtaaaga tactagcggg aggggagaaa gctcaaatga 240
ctctgtaatt tagaattaca accagagaag aaatacttca agcacaataa agacgttcca 300
ttgaagagcg acattcattc tggaatqttt qttttgaaaa caactcttnt qqqqqaattc 360
aaaaggtact gaacaaagca acataaagta agttttgggt tgttttgcaa aataaaaata 420
tacaattgag tggaccagat ggcaaaaaca taccaattac aatctgaatg ctatatttaa 480
aacccttaaa ttctgaaggc ctgaatatca acaaacctat ttatgtttat gatcctaaaa 540
agacattaaa tattattaaa cccccaactt ccaaaacata g
                                                                   581
<210> 472
<211> 674
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(674)
<223> n = A, T, C or G
<400> 472
gaattegaae ceetteggat ggegtgatgt nteacagaaa gtteteeget eecagacatg 60
ggtccctcgg cttcctgcct cggaagcgca gcagcaggca tcgtgggaag gtgaagagct 120
tecetaagga tgaccegtee aageeggtee aceteacage etteetggga tacaaggetg 180
gcatgactca catcgtgcgg gaagtcgaca ggccgggatc caaggtgaac aagaaggagg 240
tggtggaggc tgtgaccatt gtagagacac cacccatggt ggttgtgggc attgtgggct 300
acgtggaaac ccctcgaggc ctccggacct tcaagactgt ctttgctgag cacatcagtg 360
atgaatgcaa gaggcgtttc tataagaatt ggcataaatc taagaagaag gcctttacca 420
agtactgcaa gaaatggcag gatgaggatg gcaagaagca gctggagaag gacttcagca 480
gcatgaagaa gtactgccaa gtcatccgtg tcattgccca cacccagatg cgcctgcttc 540
ctctgcgcca gaagaagccc acctgatgga gatccaggtg aacggaggca ctgtggccga 600
gaagctggac tgggccccgc gagangcttg agcacaggta cctgtgaacc aagtgtttgg 660
gcaggatgaa aatg
                                                                   674
<210> 473
<211> 646
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> (1)...(646)
<223> n = A, T, C or G
<400> 473
ttttttcagn ggaaaataac ttttattgan accccaccaa ctgcaaaatc tgttcctggc 60
attaagetee ttntteettt geaatteggt etttetteag nggteeeatg aatgetttet 120
tetecteeat ggtetggaag eggeeatgge eaaaettgga ggnggtgtea atgaaettaa 180
ggtcaatett etecanagee egeegntteg tetgeaceag eaaggaettg eggagggtga 240
gcaccegett ettggttece accacacage ettteageat gacaaagtea ttggteactt 300
caccatagng gacaaagcca cccanagggt tgatgctctt gtcanatagg tcatagtcag 360
tggaggcatt gttcttgatc agcttgccgt ccttgataag gtagccctgg ccaatcttat 420
aaatottett gttgatetea gtgeggtgat ggtageettt etgeeeageg egtgeeacag 480
agaaggctac acgagcagga tgccatgccc caatacaggc caccttgcgc aggcctcggt 540
gggtcttgcg gggcagcttc ttggtgtgcc aacgactggt gacccctttg tagcctttgc 600
ccttggtcac cccgatgacg tcgatcatct catcctgccc aaacac
<210> 474
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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\langle 223 \rangle n = A, T, C or G
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gcagcacggc acagcacgct cgacttcatg ctcggcgcca aagctgatgg tgagaccatt 180
ctaaaaaggcc tecagtecat tttecaggag caggggatgg eggagteggt geacaectgg 240
caggaccatg gctatttagc aacctacaca aacaagaacg gcagctttgc caatttgaga 300
atttacccac atggattggt gttgctggac cttcagagtt atgatggtga tgcgcaaggc 360
aaagaagaga tcgacagtat tttgaacaaa gtagaggaaa gaatgaaaga attgagtcag 420
gacaagtact gggcgggtga aacgattacc acccatagtg cgaggaggag ccatcgacag 480
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gacg
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<210> 475
<211> 578
<212> DNA
<213> Homo sapiens
<220>
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<222> (1)...(578)
<223> n = A, T, C or G
<400> 475
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ctcacagggc agacccctgt gttttccaaa gctagataca ctgtcagatc ctttggcatc 180
cggagaaatg aaaagattgc tgtccactgc acagttcgag gggccaaggc agaagaaatc 240
ttggagaagg gtctaaaggt gcgggagtat gagttaagaa aaaacaactt ctcagatact 300
ggaaactttg gttttgggat ccaggaacac atcgatctgg gtatcaaata tgacccaagc 360
attggtatet acggeetgga ettetatgtg gtgetgggta ggeeaggttt cageategea 420
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```
gacaagaagc gcaggacagg ctgcattggg gccaaacaca gaatcagcaa agaggaggcc 480
atgcgctggt tccagcagaa gtatgatggg atcatccttc ctqgcaaata aattcccqtt 540
tctatccaaa agagcaataa aaagttttca gtgaaaaa
                                                                   578
<210> 476
<211> 619
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (1)...(619)
<223> n = A, T, C \text{ or } G
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tettececeg taaggaaatg geeggggage teeaggggae eeaggegeeg tegettegge 120
ggagcctggg ctgaccagcc aggacagcgg ggtaaacccg aacaattctg cgcgaggtag 180
ggaggccatg gcgtccggca gtaactggct ctccggggtg aatgtcgtgc tggtgatggc 240
ctacgggagc ctggtgtttg tactgctatt tatttttgtg aagaggcaaa tcatgcgctt 300
tgcaatgaaa tetegaaggg gaceteatgt ceetgtggga cacaatgeee ceaaggaett 360
gaaagaggag attgatattc gactetecag ggtteaggat ateaagtatg ageeceaget 420
ccttgcagat gatgatgcta gactactaca actggaaacc cagggaaatc aaagttgcta 480
caactatctg tataggatga aagetetgga tgccattcqt acetetgaga teccatttea 540
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gatcttgcga aacactagt
                                                                   619
<210> 477
<211> 674
<212> DNA
<213> Homo sapiens
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ttaaagagga aaaagcaagt tgctccagaa aaacctgtaa agaaacaaaa gacaggtgag 180
acttcgagag ccctgtcatc ttctaaacag agcagcagca gcagagatga taacatgttt 240
cagattggga aaatgaggta cgttagtgtt cgcgatttta aaggcaaagt gctaattgat 300
attagagaat attggatgga tcctgaaggt gaaatgaaac caggaagaaa aggtatttct 360
ttaaatccag aacaatggag ccagctgaag gaacagattt ctgacattga tgatgcagta 420
agaaaactqt aaaattcqaq ccatataaat aaaacctqta ctqttctaqt tqttttaatc 480
tgtcttttta cattggcttt tgttttctaa atgttctcca agctattgta tgtttggatt 540
gcagaagaat ttgtaagatg aatacttttt tttaatgtgc attattaaaa atattgagtg 600
aagctaattg tcaactttat taaggattac tttgtctgcc cacccctagt gtaaaataaa 660
atcaagtaat acat
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<210> 478
<211> 663
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1)...(663)
<223> n = A, T, C or G
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cctgctcagt tttcacacaa gccatgttgt ttatcaaatt agatctgcta atattgaata 240
cagtagattc ggtgattgta gttctcatat aagtatctta ttgagataac attttgacag 300
tttcactgac tttccaaata agcataccat aatcaaagaa aagaataaag agtgaagtaa 360
aaccattggg ggtggaagtc aaacaagcct agacatttga ttggaagaga aaagatcaaa 480
tatgaagttc acaaaccaaa agtttataaa ctcaatgcaa tacaaatcct ttttattgta 540
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cta
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<211> 673
<212> DNA
<213> Homo sapiens
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teettaacaa ggaaateace agtgtgggea gtteeaageg ggaagaggag geeaagteag 180
aacttcgagc agccattgat cggtatgtgc aagagaagat tgtgctagca gctcaggcaa 240
tttcacgctt tgcttaccag aagatcagta atggagatgt gatcctggta tatggatgct 300
catctctggt atcacgaatt cttcaggagg cttggacaga gggccggcgg tttcgggtgg 360
tagtggtgga cagccggcca tggctggaag gaaggcacac actacgttct ctagtccatg 420
ctggtgtccc agcctcctac ctgctgattc ctgcagcctc ctatgtgctc ccagaggttt 480
ccaaggtgct attgggagct catgcactct tggccaacgg gtctgtgatg tcacgggtag 540
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gaccctgatg atc
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<210> 480
<211> 203
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(203)
<223> n = A, T, C or G
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gatgaagaag aggangaaga tgangananc teeteggagg gettggagge tgaggaetgg 120
gcccagggag tagtggaggc cgntggcagc ttcggggctt atggtgccca ggaggaagcc 180
cantgcccta ctctgcattt cct
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<210> 481
<211> 482
<212> DNA
<213> Homo sapiens
<400> 481
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atctcttaag tatccttacg ttgcagtgat gctaaaagtg gcagatcatt caggccaagt 180
aaagaccaag tgctttgaaa tgacgattcc acagtttcag aatttctaca qacagttcaa 240
ggaaattgct gcagttattg aaacggtgtg aagacggatt ctttggttga taaattgcta 300
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tcattctaaa gtcatggact tcactttcgg caacaaaact aaataaggat ggaacattta 360
ttgaatgaaa aatgcacttt tgtttttcca tttttttaaa taataaaaat cagacaaaca 420
gaaaaaaaaa aaaaaaaggg cggccgctcg agtctagagg gcccgtttaa acccgctgat 480
ca
                                                                   482
<210> 482
<211> 505
<212> DNA
<213> Homo sapiens
<400> 482
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tgtagaaccc agtgtgagca agatttgggt accctacata cattcagtag ccaqqaaagq 180
gtgattggat tgccagactc tgcctgctgg caaaaggatg agctgtagaa gctgaagtcc 240
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atttggaatt gaatttttcc tctaattatt ctagggaaac cctgggctaa gaaaccaatg 360
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attettaaga atgeeteea ggegeetgga agatgaaact ttetggtgaa tatgagetea 480
tggtaaaaat ttaggtcgga tgcag
<210> 483
<211> 501
<212> DNA
<213> Homo sapiens
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ttcaagtggg caagctgggg tttttaggta gtcagtggcc tagttcctaa agccacagta 180
taggatetgt taaactgaat gtetgttgaa agtttgtttt agetgettgg aggetteett 240
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ctggccagat aactgcctga tttctcagat attatttctc tgggaaacat tctacatagc 360
acaggagett aagagtggca ttatettete geettaattt eeagagatta tttetgtaet 420
gagaatcetg gaactactat getaggaaat ttaaagetge atggtetgte ttgtttteat 480
ttaattattg tgaataccta g
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<211> 501
<212> DNA
<213> Homo sapiens
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ccgcctctca cttcagaaac gtcatctttg acatcacgcc gggagatgag gcaggaaagt 240
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tcaatgtcaa cetteteate tteeteetea acaagaagtt tttgeggaag tgacagagge 420
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<210> 485
<211> 504
<212> DNA
<213> Homo sapiens
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ctaggatttt ctctattgtt ttatgcttat tttgatattt gattcctaga attttaaata 180
cattatatat catataaaat aaacetttaa atattgaaat gaaaagataa aaatacatac 240
actaagtgaa taggtcaaaa gtgtgagatc atcttgaaca ttatcttgaa qagaagatac 300
caatttacct tctgctcaga tcatggtgta cgatatcaca acctgcctag aataactctc 360
cttttctgaa ccatttattc actacttttg tcttccaatt aaatattagc ctgacttcaa 420
atatcataca ttagtttcct ttgtttatgt aattgaatta tataacatat attcattaga 480
gcctattttt tttaaaattt ttgt
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<210> 486
<211> 501
<212> DNA
<213> Homo sapiens
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gcacggacgc accaaggagc agaaggggcc cctgtcgggt gcagcgtcct gggagcatat 240
caaggetgtg eggaaggetg tggeeateee tgtgtttget aaegggaaea teeagtgeet 300
gcaggacgtg gagcgctgcc tccgggacac gggtgtgcag ggcgtcatga gcgcagaggg 360
caacctgcac aaccccgccc tgttcgaggg ccggagccct gccgtgtggg agctggccga 420
ggagtatetg gacategtge gggageacee etgeeceetg tectaeqtee gggeecaeet 480
cttcaagctg tggcaccaca c
                                                                   501
<210> 487
<211> 501
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1)...(501)
<223> n = A, T, C or G
<400> 487
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caacccctat aaagggtagt tcttttaaaa aaaatttctt tattggcaac aacataaaag 180
atatgaaaga atcactcata atttatcagc ataacatagc tattctcatt tttgcaattg 240
actttttagt tcttgaccaa atgtaatttt tattagttgt gattaactga ttttgtgctt 300
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tgtattcatt ctgtttatgt accataattt tggatgttcc tacgatgtta aacttttagg 420
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ggagaatgtc aaagaagtcc t
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<210> 488
<211> 148
<212> DNA
<213> Homo sapiens
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ggacagaggt ggaattgagt gtccacaggc cagctgagga ggtggtaccc agcactctat 120
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<212> DNA
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ggagccactc tacggattca tggtgtaaat tctggatctt ctgaaggagc ccaaccaaat 180
actgaaaacg gagtccctga aataacagat gcagccacag atcagggccc tgcagaaagc 240
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gagagaactg tttccttgtc tcagatgtta agggaagcta aggagaagga gaagcagaga 480
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                                                                   501
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gcagtcactc aggtttattt ccaccagggc ccaagaaaaa aagaaatgag gcaacctaaa 360
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<211> 483
<212> DNA
<213> Homo sapiens
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cag
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<212> DNA
<213> Homo sapiens
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aatggaccaa atgtgccaca cgctcgctct tttttacacc cagtgcctct gactctgtcc 180
ccatgggctg gtctccaaag ctctttccat tgcccaggga gggaaggttc tgagcaataa 240
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<212> DNA
<213> Homo sapiens
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ctttctatac ctttgtacta tgcactgccc tattgattct acacccaata atgatattac 180
ttgaacccat ctgtaagaaa ctgcttcgga aattcatttg tgtgtatgta aataacacaa 240
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tattttcggt tttgctttaa gtccttttat ttttaattcc ctttttgttt ttcttttgg 360
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<213> Homo sapiens
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agetgeggae gaegegggt ccateagege geegggetge egeetetegg ceaeggetgg 180
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gtcg
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<211> 471
<212> DNA
<213> Homo sapiens
<400> 498
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taaaacaaaa ttgattttaa aatttttatg taagtcattg tgtctatgat gccactttta 360
aaaggaaaat gcaattgcgt aatggcttat atccttattt aatgtaccta tttgtgttct 420
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<210> 499
<211> 478
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<213> Homo sapiens
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eccgcaggge egeteegegg ggcagegeag ecaggeegge tatggteeeg gggeteeege 180
cgccccccag gtgcccggga cccgccaggc cggtgcgcga gggtcacccc acctccccgc 240
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214

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ccaataagga aaagcttgaa gccaccatta atgaattagt ctaatcatgt tttctgaaaa 360
tataaccagc cattggctat tt
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<211> 323
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<213> Homo sapiens
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<222> (1)...(323)
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<211> 605
<212> DNA
<213> Homo sapiens
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<211> 565
<212> DNA
<213> Homo sapiens
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<211> 642
<212> DNA
<213> Homo sapiens
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<221> misc feature
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ttcctagttt caggaatccc ccaaatcact tcctcattgg cttagtttaa agccaggaga 180
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gtcaccttcc tgggggcctt ggctttgatc tacaatgaag ccctcaaggg ctgaaaataa 180
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<210> 524
<211> 407
<212> DNA
<213> Homo sapiens
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gtgtcctttt atttcctgtt gatgataaag aatcaagaaa caaagggcaa gatttgttgg 240
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<211> 276
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(276)
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aagctggttt tctagacctg ttagctggaa gcatggtgag caccatttct ggacgctcag 240
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<210> 526
<211> 288
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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<211> 489
<212> DNA
<213> Homo sapiens
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tcataattta gggacattct cttctagtaa gcatggtgca ttatttacta gagatataat 180
atgcattaaa acaaaaaatg ttttctatca tcatagaaaa gtttgaggtc cagggataat 240
catctctgga tacattattt cctaccgtcg tggtacacac tgaacacatt tgaggcttat 300
gactggttct tttacttaca aatattgttt agacacattt tcaaatgtca caccaatcaa 360
taataataag gaatggattt tatctatatt gacagttctt tcaaccttaa gagtgaactg 420
ctacaggtaa gattcaatca catttttcag gagaaagcta ttgagaccaa tatgctttgg 480
ttatctaata ggggtggaat gacttataat gctatttact ccaggcaaag agaaaataca 540
acagacatag gatettgatt teaaegtagt teteeteeat gtgeatttet etgteegttt 600
aggcaatgcc aactggtcca ccagtgaaca t
                                                                   631
<210> 530
<211> 316
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1)...(316)
<223> n = A, T, C or G
<400> 530
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ttgttgttta tcgaaagata ttcaaggaga aagatctgac tctccaaact gcatctgaga 120
ttgccacttt aaacagacct catttcaaac atgcaacaac gccactggta ataaagcttt 180
ggaatgggtg ctcattctat tatttcacta caaacagcat agaaagcaag agaagttggg 240
aatttattct aaaatagaat ggaggttgtc atctacagca gcactcctca ctcctctgtt 300
gccattttta gcaagt
                                                                   316
<210> 531
<211> 296
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (296)
<223> n = A, T, C or G
<400> 531
aaagtatcat ttatttgaaa aacatacatt atcattntgt ttttgatatt tgataatgaa 60
aaaaatcttt gnttgtttat ttctgaaaaa gaactgtatt tagngattat tttagatagt 120
gatattatan cattcatctg tgtgtaaatt atttcatata gggaagagtt ctgatctgta 180
cctatggttc ttattgaaaa caacattgga tgtgcatttc tgtgatgtta tgaatacatt 240
tctactttat tttgaaacat ttgccaaact aaatactgta acactgtata acattt
<210> 532
<211> 266
<212> DNA
<213> Homo sapiens
<400> 532
acatatgcac caaattccat tttagaagtt tccatatcat tttcatagaa aacaaagttt 60
gaaaacaagt aacatttaaa cacagcacgg tattctacca caactgaaac ttttttcttc 120
ttcttcttta caggactcaa caaaatctaa aaatgaacta tgctgtagat ttacctcatg 180
caaagatett tatgttatet etgaaaatga aaaggatgge ettttaagea cattttaetg 240
ttttatacta ttatggcaac ttgtgt
<210> 533
<211> 289
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(289)
<223> n = A, T, C or G
<400> 533
actcagaagt cacttttaat atcancgaca gaaatatttc actaattcaa ctgaggcaaa 60
tttcctttct agacaaagga cctagaaatt gagcatgcaa aacatccatc cattcattca 120
ttcaaataat tagccaattt taccgtcatt taattccacc agaagcaaat actagaatat 180
ctagaagtag tttgggtaaa gaaacattta cattttaata ttgtgtaatg tcataaattt 240
```

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289
ggggctaaaa taacaccagg tcaaatttga tccctttgta tqtqaqqqt
<210> 534
<211> 293
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(293)
<223> n = A, T, C or G
<400> 534
aaaataaaag gttctttaca agatgatacc ttaattacac tcccgcaaca cagccattat 60
tttattgtct anctccagtt atctgtattt tatgtaatgt aattgacagg atggctgctg 120
cagaatgctg gttgacacag ggattattat actgctattt ttccctgaat ttttttcctt 180
tgaattccaa ctgtggacct tttatatgtg ccttcacttt agctgtttgc cttaatctct 240
acagccttgc tctccggggn ggttaataaa atgcaacact tggcattttt atg
<210> 535
<211> 408
<212> DNA
<213> Homo sapiens
<400> 535
acttgaacac ttaaagagaa aaactctaaa taaagtcata gaggggatgg tagagatgac 60
cacagaaaat gaccacggag agtattatga agattgcaag attagacatt gatgatgtaa 120
attactccct ttctagataa aataatccat agatgtttat gaatcatatt tgtatgatta 180
ttgctgttac tattattttg acacattatt tattattatt gttgtcacta ttattaccat 240
taagatagca ggcgtaaaac tgtactggtt ccttcagtag tgagtatttc tcatagtgca 300
getttattta tetecaggat gtttttgtgg etgtatttga ttgatatgtg ettettetga 360
ttcttgctaa tttccaacca tattgaataa atgtgatcaa gacaaaaa
<210> 536
<211> 184
<212> DNA
<213> Homo sapiens
<400> 536
acctctcatc aaggctctgc ctacaggcac attgtgatgt atctctgcac tgatcaccta 60
ggtcatgtaa cttttttcta ggctctacct acgatggcat tgtgacataa ctctgcacta 120
atcatccacg tgatgtaact cttgtctagg atgtgcctaa attaactttt tgacgtaacc 180
ctgt
                                                                    184
<210> 537
<211> 311.
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(311)
<223> n = A, T, C \text{ or } G
<400> 537
ccacagttgt atcatatagc atctntaaca tttcatctag gattatctag tatagatctt 60
actatatttg gggctatgtt gtatacaatg ttaacaagaa catatcttct ctgcatatat 120
gtgtgaatta taaagaaaag catgagaatg actctaagtt caacaaacat gggtgaatct 180
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ctatgtgctc ccagtgtcct ggatgggctc cccagcaagc cattcctcct tcctgttctg 240
atattactat tcttttttac attgtgctaa ggaggacaaa aggtgagaga tgaaaataaa 300
gccttgcctt t
                                                                   311
<210> 538
<211> 302
<212> DNA
<213> Homo sapiens
<400> 538
aaaataaaaa agcaaaaact cttgtggtac ctagtcagat ggtagacgag ctgtctgctg 60
ccgcaggagc acctctatac aggacttaga agtagtatgt tattcctggt taagcaggca 120
ttgctttgcc ctggagcagc tattttaagc catctcagat tctgtctaaa ggggtttttt 180
gggaagacgt tttctttatc gccctgagaa gatctacccc agggagaatc tgagacatct 240
tgcctacttt tctttattag ctttctcctc attcatttct tttatacctt tcctttttgg 300
<210> 539
<211> 396
<212> DNA
<213> Homo sapiens
<400> 539
actgtttatt tgctccttct cttcatgcct gtggctggat gtcccacaac actataagaa 60
atataagtca agccctttgt gttaagcaag aactacagac tecatetttt cacccaaate 120
atgaatgacc aataaaaagc aagttattcc agaggaagaa gcagcccttg aaatgttaag 180
gettaggett gaaaggtgaa gageaggaat tetetettte aaateetaga geataaacee 240
atgtgtggcc aagtgagate agcceteaag ggcacatgce aagggeagag cageecatgt 300
agacagette ggagggeatg ggggtgtagg gagttegggg tageteetea ttaactattt 360
gttgggtgag taaaggggtg aggctcagtg gcaggt
                                                                   396
<210> 540
<211> 634
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(634)
<223> n = A, T, C or G
<400> 540
ccaaaaacaa gatgaccaga tttgntttna gcctgatgac cctacaggtc gtgctatgat 60
atggagtect catgggtaaa gcaggaagag agtgggaaag agaaccaccc cactctgtct 120
teatatttge attteatgtt taaceteegg etggaaatag aaageattee ettagagatg 180
aggataaaag aaagtttcag attcaacagg gggaagaaaa tggagattta atcctaaaac 240
tgtgacttgg ggaggtcagt catttacagt tagtcctgtg tctttcgact tctgtgatta 300
ttaaccccac tcactaccct gtttcagatg catttggaat accaaagatt aaatccttga 360
cataagatet catttgeaga aageagatta aagaceatea gaaggaaatt atttaggttg 420
taatgcacag gcaactgtga gaaactgttg tgccaaaaat aqaattcctt ctagtttttc 480
ttgttctcat ttgaaaggag aaaattccac tttgtttagc atttcaagct tttatgtatc 540
catcccatct aaaaactctt caaactccac ttgttcagtc tgaaatgcag ctccctgtcc 600
aagtgccttg gagaactcac agcagcacgc ctta
                                                                   634
<210> 541
<211> 221
<212> DNA
<213> Homo sapiens
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<400> 541
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atggaagggg ctcctgctca cagcatcact tttaaacttc tggaacctgc ccaccactgc 120
ccaagtcacg attgaagccg agccaaccaa agtttccgag gggaaggatg ttcttctact 180
tgtccacaat ttgccccaga atcttaccgg ctacatctgg t
<210> 542
<211> 287
<212> DNA
<213> Homo sapiens
<400> 542
cctcttctac tatggcagga gatgtggcgt gctgttgcaa agttttcacg tcatcgtttc 60
ctggctagtt catttcatta agtggctaca tcctaacata tgcatttggt caaggttgca 120
gaagaggact gaagattgac tgccaagcta gtttgggtga agttcactcc agcaagtctc 180
aggccacaat ggggtggttt ggtttggttt ccttttaact ttccttttgt tatttqcttt 240
tctcctccac ctgtgtggta tattttttaa gcagaatttt atttttt
<210> 543
<211> 274
<212> DNA
<213> Homo sapiens
<400> 543
acttgtgaaa cacagetgtt ettetgttet geagacaege etteeeetea geeacaecea 60
ggcacttaag cacaagcaga gtgcacagct gtccactggg ccattgtggt gtgagcttca 120
gatggtgaag catteteec agtgtatgte ttgtateega tatetaaege tttaaatgge 180
tactttggtt tctgtctgta agttaagacc ttggatgtgg tttaattgtt tgtcctcaaa 240
aggaataaaa cttttctgct gataagataa aaaa
<210> 544
<211> 307
<212> DNA
<213> Homo sapiens
<400> 544
ccaggtggtt gtcttattgc accatactcc ttgcttcctg atgctgggca atgaggcaga 60
tagcactggg tgtgagaatg atcaaggatc tggaccccaa agaatagact ggatggaaaq 120
acaaactgca caggcagatg tttgcctcat aatagtcgta agtggagtcc tggaatttgg 180
acaagtgctg ttgggatata gtcaacttat tctttgagta atgtgactaa aggaaaaaac 240
tttgactttg cccaggcatg aaattettee taatgteaga acagagtgea acceagteae 300
actgtgg
                                                                   307
<210> 545
<211> 570
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(570)
<223> n = A, T, C or G
<400> 545
accttagaaa tttgcaacca cctccctgaa agtcttctcc cacgttatta agtgcaatgt 60
ttatggtaaa tgtagaagca tcatgatgag gacgaagaga acgctgtcgt tcaggggagt 120
attttactac aaaattcagt agtgcaaatc ccttcgtata atagcctgca aagaccttca 180
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gtgtaactgg ngcaatgaac tcccggataa aatgaagcca tacattctcc agatcaactt 240
gcttcatgtg gatatcatca gttgggacat tttcataacc accagatata cggctatcat 300
gatgttttcc cccagaccat ttgccgtaat gttccatttc ttctaccaat tcatcacagg 360
ctttttcaga aaatatgggg aaccaaaaga catctggaca gggctgttca actatatttt 420
cagtgaaaat ctttgaataa tcacggttta tatacttttc cttccagtcc acaggatttt 480
caaaaatctg ccagaggtca ttgttataat gggaagtatt gtaattagca gtggataata 540
gccttccaaa ttcatgtcta ttagaaatgt
<210> 546
<211> 589
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(589)
<223> n = A, T, C or G
<400> 546
aaaaatactt tttaccaaag gtgctatttc tctgtaaaac actttttttt ggcaagttga 60
ctttattctt caattattat cattatatta ttgtttttta atattttatt ttcttgacta 120
ggtattaagc ttttgtaatt atttttcagt agtcccacca cttcataggt ggaaggagtt 180
tggggttett cetggtgeag gggetgaaat aacceagatg cececaceet gecacatact 240
agatgcagcc catagttggc cccctagct tccagcagtc cactatctgc cagaggagca 300
agggtgcctt agaccgaagc caggggaaga agcatcttca taaaaaactt tcaagatcca 360
aacattaatt tgtttttatt tattctgaga agttgaggca aatcagtatt cccaaggatg 420
gcgacaaggg cagccaagca gggcttagga tatcccagcc taccaatatg ctcattcgac 480
taactaggag ggtgagttgg ccctgtctct tcttttttct ggacctcagt ttccttcagt 540
ggagcttggt aaaaatgcac taccntttga tttgataagg tataaatct
<210> 547
<211> 293
<212> DNA
<213> Homo sapiens
<400> 547
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tacccttatt ttactgacca atatggaagt tcttggtatc tttaaggetg accttcctgg 120
tattgtgtaa tgattgaatg tatctaaact gtaataattt gaaactgaca aacataacct 180
tctcagactt acaaaactat gttctttcta aagatacaga tttttattat tttattttga 240
ctaggaagga tttataaata aatgtaatga aaaatctttg atcttaataa agt
                                                                  293
<210> 548
<211> 98
<212> DNA
<213> Homo sapiens
<400> 548
aaacaaaggt tgagatgtaa aaggtattaa attgatgttg ctggactgtc atagaaatta 60
cacccaaaga ggtatttatc tttacttttt tttgtaca
<210> 549
<211> 121
<212> DNA
<213> Homo sapiens
<400> 549
acatgcatat ttcaaagacc tgttaatggc gtccactttg gattcttaca tgaaacgatt 60
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cagtgcacat tgtaagccta aggaccacgc aaaagggttt cccacatatt aagtattcag 120
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<211> 509
<212> DNA
<213> Homo sapiens
<400> 550
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tactacaata gttttatgca caacttccca ttaaaaaatga gatttcttat ttgtttgtct 120
gtttttactc tgggagtaat actttttaaa ttacctttac atatatagtc actggcatac 180
tgagaatata caatgateet ggaaattgea gtaacaaaag cacacaacga ttatagtaac 240
tataagatac aataaaacaa ataaatgtga aagtagattc atgaaaatgt attcctttaa 300
aatattgttt tcctacaggc ctatttaaca agatgtttca ttttactgta tattttgtag 360
ttaatataaa tgttgctcta atcagattgc ttaaaaagcat ttttattata tttatgttgt 420
tgaactaata tatgaaataa gtaaatgtag ctcccacaag gtaaacttca ttggtaagat 480
tgcactgttc tgattatgta agcatttgt
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<210> 551
<211> 427
<212> DNA
<213> Homo sapiens
<400> 551
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aaaagaagct taagttttat catccttttt tttctcgtga attcttaaag gattatgctt 120
taatgctgtt atctatctta ttgttcttga aaatacctgc attttttggt atcatgttca 180
accaacatca ttatgaaatt aattagattc ccatggccat aaaatggctt taaagaatat 240
atatatattt ttaaagtagc ttgagaagca aattggcagg taatatttca tacctaaatt 300
aagactetga ettggattgt gaattataat gatatgeece ttttettata aaaacaaaaa 360
aaaaaataat gaaacacagt gaatttgtag agtgggggta tttgacatat tttacagggt 420
ggagtgc
<210> 552
<211> 340
<212> DNA
<213> Homo sapiens
<400> 552
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ctgtcaagag aaatggtcca ccgtgtgtgt ggaatgcagc catcacacat tagtttctqa 120
gattgcttct gtcttggttt tatggggaga tatttccatt tctagcatag gcttcaaggc 180
getetaaata teegettgga aatactacaa aaacagtgtt teaaaactge tgtatecaaa 240
ggaaggtgcc actcgctgag ttgaatgcac acatcacaag gaagtttctg agaattcttc 300
tgtctagatt catacgaaga aatcccgttt ccaacgaagg
<210> 553
<211> 549
<212> DNA
<213> Homo sapiens
<400> 553
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ggggtcacta tggagttcaa aggacagaac tcctgcctgg tgaccgggac aacctggcca 120
ttcagacccg gggtggccca gaaaagcatg aagtaactgg ctgggtgctg gtatctcctc 180
taagtaagga agatgctgga gaatatgagt gccatgcatc caattcccaa ggacaggctt 240
cagcatcagc aaaaattaca gtggttgatg ccttacatga aataccagtg aaaaaaqgtg 300
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gataactaca tagttatatt	ttacctgttc cactggtttt	ttgcctaata acacagagaa	agtttctttt atacaaaata	aatccaatcc aagatcacac	agtagtcatg actaacactt atcaagacta aacaaataaa	420 480
<210> 554 <211> 321 <212> DNA <213> Homo	sapiens					
actgaaaatg tttataaagt gaattctgag tctacgcaag	aagttaccat aaattcagat tcaataacta	tcctaggcca atgcttacaa aaaaccattt attgagtcaa	aatttttaga taaaaagaca ctaccagtgc	caaagctttc taaaagattc atcactacca	ccccttggca taaaaccatc atcctgagat tgtaatccat aagacccaat	120 180 240
<210> 555 <211> 322 <212> DNA <213> Homo	sapiens					
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<210> 556 <211> 286 <212> DNA <213> Homo	sapiens					
cgggccctcc ttttgctgcg tcagaggcat	tcttcaggaa gccccgtggg	tcttcctgaa gtaggaggga ggcacaattc	gacatggccc cagagagaca ttcggatgac	agtcgaaggc gggagagtca tgcagaaaat	gcaggtattt ccaggatggc gcctccacat agtgttttgt	120 180
<210> 557 <211> 459 <212> DNA <213> Homo	sapiens					
aaaacaggta tgttcaggtt gaagtgtata agccaagcat agtttttaa gagacttcac	aatataatga taaatactaa caagtgcatt atgtctacat aaagtttcat	ctattactgt gcacaaaaat gcaaatgagc ttatgatttc catggctgtc tctcctttct	taagaaagac ataacaaatt tctttaaaat tttctcttat atcttggaat gggtgcatct	aaggaggaaa ctgtgtctac ttaaagtcca tttaaagtct ctagcctcca	attgtgttaa actgtttcaa aataatttt tttccccttt cttctggttt gctcaaagct tctccaagta	120 180 240 300 360

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<210> 558
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(303)
<223> n = A, T, C or G
<400> 558
aaaaaataaa aaacaagaca acaatttagt agaagtaccn ctgggaggga ggggagggga 60
aaaaaggata tacaggggca ggngtattct ctgtacagag gtgcananaa aatttcacat 120
anctttanag aatgeettgt ggaaaaaaaa aaataggeee caataettgt taetgeeett 180
tatcaaaact gtgtgcatga cctgcacaaa taaaatcaca aaacagtgtt gccacattct 240
tcaaggaaac aaagcaaaat ttagggggnt tcttttccct ctccttgtta aaagtcattt 300
<210> 559
<211> 232
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(232)
<223> n = A, T, C or G
<400> 559
aaagcattta ttaagaattt actcaggcat gatggcccat acttgtaatc ccagctattg 60
ggaaggatga gatgggagga tggcttgagg ccaqaggttt qaqaccqacc aqccaqqqca 120
acacagtgag acceettete aaaaaaaaaa aaaaaaaaag agagagtgtg tgattagaag 180
ctaaatagga aagttttgag cttcaagtca gngaggagta aaaaagattt tt
<210> 560
<211> 336
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(336)
\langle 223 \rangle n = A, T, C or G
<400> 560
ctctgcaaaa ataannataa aaaaataaat aaaattttaa aaataataaa attcactata 60
tacacatata aagaaataaa aagaagtctc agttgcagct atttgtcaaa attaatatcc 120
atttcttttt atatacggtg aatattgcgc aattatagat ctggattttg aaccacttaa 180
tgaagcggca acaccaggtg ttttgaggtg ttggcattct tcgctgattt ggctgttccc 240
aatgtttaca ttatttaatc ttgcaaaaat ggttctgtgc acttggatgn gaaatgctgn 300
ccagnittat tittittatg tigntatcct tggatg
                                                                    336
<210> 561
<211> 636
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (1)...(636)
<223> n = A, T, C or G
<400> 561
acattatggg ttttattgct ttcttttatg gtagacctgt taatggggaa aaaatacatc 60
aaatcaaata gaatcttata tetgtatgtt aaaatagage aettaeetga agteagtgge 120
ctggatcata gccctggatc atttcccagt ctgtcctgtg ctgtgtgacc ttggacaagg 180
cgcttcatct ctctgggcct ctatttctcc atttgtaaaa caagtggctg cagtagatga 240
tggctgagag cccttcctgt tcccagatgc cttggtccaa agaccccacc cctctgctgg 300
tectgecaae gtgttggtge tataagetge tteagatata aaattggttt atetataatg 360
tttgttcatt taatagcttc taaaaggcct ttttgttata cagtgctttt tttctagttt 420
tatggacttg gttactgtaa taatgtcttg tttttagcca tgtaactaca aacagatatt 480
ctcttgatgt cttagtaaat ttgcatttga tatatcattg atgagatttt gttgttatgt 540
aatattettt ggetaegeat etgteeagea tettattaae cataataetg ngateattat 600
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                                                                   636
<210> 562
<211> 708
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(708)
<223> n = A, T, C \text{ or } G
<400> 562
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tcacaatgac attccatagt aaatttggaa tcagaactcc aaatgcaact tcgggctcgc 120
tggagaacaa ctaaggggca ccaaaccctc tgaggtttta ctttaaggtt cgctgtatgt 180
ttgccttgga caaaaagget acctaccacg tgctatccag taatatactt aaataagcca 240
atacttagat ctactgtaag gcagatgcta attataaggc attaagtaag caaatagtgc 300
cctcagctac tgcagaagaa aagtcccact gaggaaaaga aagtcttgtg atttttaaag 360
gcaagttttc aagtgctctc atagttctat cctctaattc cattaaatcc atactaggag 420
cgtcagtgag ggttttcata gcttttggaa atactttggt ctctgaactg taattagcaa 480
gaagtaaaaa cagaaacgtc aaacgtcaaa tgtttgcttt gttacctgga ggactaaatg 540
tagatgtett tagtataett tgtatgttet taatattgga agataatttt gtgaatetgt 600
agattttatt ttttcagtct taccttacaa atttcttttc tatgaataat agaggactta 660
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<210> 563
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<212> DNA
<213> Homo sapiens
<400> 563
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ctgtataata ggcttgagag atateettea tttgeetget tgteetggta gttaagattt 180
caatcaagge atettegttt gtteeegege eetteatgga tttetttage tgetttgeat 240
caaagactgc tggtggagtc actagggcca ccatgagatg ctcaaagtgg
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<210> 564
<211> 530
<212> DNA
<213> Homo sapiens
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<400> 564
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accatacgct ccaaaagatg gctgtgatag atcttgtgaa gcaattactg agcagatcaa 120
gatctttggg aaggaacact aaagatgttt tgaatgaatt atagtccact ggcattttag 180
tgtatttttt tttcttttta gaaacacaca tttctaaaaa tgtcatgtta cattcctgca 240
tgtccctttt gatagcatta gtggatccat tggatttctt ttttcttttt gtgagacagc 300
ttttagtctt acctgaattt atgtgtgttt ttccgacagt ggttaataat tatattggtg 360
atgtagcagc aattgtgttg gcagggtttt catatattat tagtaattaa cactaactgt 420
tggactgact tgtgtcgata gcgctcacgc aagcatggtt aacgtcccta aaacccgccg 480
gactttctgt aagaagtgtg gcaagcacca accccataaa gtgacacagt
<210> 565
<211> 450
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(450)
<223> n = A, T, C \text{ or } G
<400> 565
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gtgtgttaag tttttcatct gtgcatcaaa tcacaaaaag aataaataga gctttttcct 120
ttatcagtcc cttgggcaca gcaggtcctg aacaccctgc tctacaatgt tgcatcaaga 180
gttcaaacaa caaaataaaa aatattaaga ggaaatcccc atcctgtgac ttgagtccct 240
taagtetaca ggggetggtg acetetttt getaatagga aaateacatt actacaaaat 300
ggggagaaaa ctgtttgcct gtggtagaca cctgcacgca taggattgaa gacagtacag 360
gctgctgtac agagaagege cteteacate tgaactgcat actgageggg caagteggtt 420
gtaagttcag taaaaccctc tgatgatgcc
                                                                 450
<210> 566
<211> 563
<212> DNA
<213> Homo sapiens
<400> 566
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ggggtcacta tggagttcaa aggacagaac tcctgcctgg tgaccgggac aacctggcca 120
ttcagacccg gggtggccca gaaaagcatg aagtaactgg ctgggtgctg gtatctcctc 180
taagtaagga agatgctgga gaatatgagt gccatgcatc caattcccaa ggacaggctt 240
cagcatcage aaaaattaca gtggttgatg cettacatga aataccagtg aaaaaaggtg 300
aaggtgccga gctataaacc tccagaatat tattagtctg catggttaaa agtagtcatg 360
tagttatatt cactggtttt acacagagaa atacaaaata aagatcacac atcaagacta 480
tctacaaaaa tttattatat atttacagaa gaaaagcatg catatcatta aacaaataaa 540
atacttttta tcacaaaaaa aaa
<210> 567
<211> 424
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(424)
<223> n = A, T, C or G
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<400> 567
ccagtgagca aattgaaaac caactgaaag caaatccaaa tgaggaagat tttaataaag 60
gaataccett ctccatagca ggtgcaatgc tgactgctca aggcgtgcgt gcgcgcgcac 120
acacacaca acacacaca atacatactc tcacacacne atetttecaa ttaaactgea 180
ggtagaatga gattttgtgt tattcaaaaa atttgtaagt gatcaaaanc actgctatgg 240
aatgeetgtt tatetgeett tgntetggtt aaaateteat aaaaataeat teaacaggaa 300
aacatanatt gtatgtgtat aaatatatat gtatatatat atattatata cacatgcaca 360
caaatacttt tgttttttga agcataagat agttacataa atactcctat aattgctaaa 420
gttt
<210> 568
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
<223> n = A, T, C or G
<400> 568
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tttgaagaag aaaggatggg aggtggtgga gtcggacctc tatgccatga acttcaatcc 120
catcatttcc agaaaggaca tcacaggtaa actgaaggac cctgcgaact ttcagtatcc 180
tgccgagtct gttctggctt ataaagaagg ccatctgagc ccagatattg tgggttganc 240
aaaagaaagc ttggaagccn caagaacctt gtgatattcc agttccccct gcantgggtt 300
tgggaagtcc ctgccntttt gaaagctggt ttgaagcgaa tgttcatagg aaagtttgct 360
taccacttac cctgcccatg gtangacaaa ag
<210> 569
<211> 559
<212> DNA
<213> Homo sapiens
<400> 569
aaagagattt attaaatcat cttatcacaa agatggaaac atatacaaac tagaaacatg 60
caaccatcat cttccacagt caagtcacaa tgtcaaatat ttttcttgcc tctgcagatg 120
aaaagttcag atcttatacc caactactta ctcaccccga atatttaagt cagtcttcct 180
gaaagtactc agggtagcaa gtaacaaaat gcaaacgatt atataaagaa agtgcagtta 240
aaaaggaaac tatgtggcaa gtaccctctt tcccttccca ccccccaatt aaaggcaaac 300
aatggcactt tgctcttgct taacctagat tgtcttcaaa aactattaaa atgtaaaaga 360
cttaacaaaa aaacaaaaag acgtttaaca gatgtcaaaa agctccttag tgtttgaaaa 420
taaatgctta aacaaaagac aacatatttt atatcaaaca agtttgaaga gccctgaatt 480
gcagcattct gtaacataaa caaacaaaaa gctggtatag gatttattgg caaaggcaga 540
atttcttcaa gcagggtaa
                                                                   559
<210> 570
<211> 368
<212> DNA
<213> Homo sapiens
<400> 570
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tgggtatggc tgtgagctca gacacttgca gatctcttaa gtatccttac gttgcagtga 120
tgctaaaagt ggcagatcat tcaggccaag taaagaccaa gtgctttgaa atgacgattc 180
cacagtttca gaatttctac agacagttca aggaaattgc tgcagttatt gaaacggtgt 240
gaagacggat tetttggttg ataaattget atcattetaa agteatggae tteaettteg 300
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gcaacaaaac taaataagga tggaacattt attgaatgaa aaatgcactt ttgtttttcc 360
atttttt
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<210> 571
<211> 261
<212> DNA
<213> Homo sapiens
<400> 571
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ttcttcgtgc ctgttttatg tgcacacatt aggcattgag acttcaagct tttcttttt 120
tgtccacgta tctttgggtc tttgataaag aaaagaatcc ctgttcattg taagcacttt 180
tacggggctg gtggggaggg gtgctctgct ggtcttcaat taccaaqaat tctccaaaac 240
aattttctgc aggatgattg t
<210> 572
<211> 488
<212> DNA
<213> Homo sapiens
<400> 572
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gtgcaagctc agcttggagg gtgatcactc tacaccccca agtgcatatg ggtctgtcaa 120
agcctatact aactttgatg ctgagcggga tgctttgaac attgaaacag ccatcaagac 180
caaaggtgtg gatgaggtca ccattgtcaa cattttgacc aaccgcagca atgcacagag 240
acaggatatt gccttcgcct accagagaag gaccaaaaag gaacttgcat cagcactgaa 300
gtcagcetta tetggceace tggagaeggt gattttgggc etattgaaga cacetgetea 360
gtatgacgct tctgagctaa aagcttccat gaaggggctg ggaaccgacg aggactctct 420
cattgagatc atctgctcca gaaccaacca ggagctgcag gaaattaaca gagtctacaa 480
ggaaatgt
                                                                   488
<210> 573
<211> 619
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(619)
\langle 223 \rangle n = A, T, C or G
<400> 573
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gaattgaaac cccagaagat aactacaaca aaaacatgtt aattttttt taaaaatgat 120
gattcaaagg cagatttgaa gggaagtaat atttaggtgg cagaagaagg caaatgcagc 180
ctctgaaggg aactgttcta attattacct aaaaaataaa gttacacaac tatattcaag 240
gacatgagat aaagcactgc ttgaaaacca gaatgactga acagttaggt gaaaaggaac 300
agctgaaata ggaaggggaa atggactgaa gaataatttg aatcgggaca gtgatccatc 360
agtectagat gettetggta tgtaaatate ttgaateaca ttgttteett tettetgaaa 420
teteaaagga gaatteteac ageaetaeat taaggttgee attttgttag gatteaaaat 480
ttcaatccag tagccatcag gatcttgaat aaatgccagg cctttcattt taccatcatc 540
aggtttcttc acaaatttga ctccagtctt caaccttttc aagcctgatc atcaggaaca 600
caattccata tgaccgatc
                                                                   619
<210> 574
<211> 202
<212> DNA
<213> Homo sapiens
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<400> 574
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cgtggaagaa gttcaaggac ctggagtagt tggtgaattt ccaatcatca gcccaggtcg 180
ggtatatgaa tacacaaqct qt
                                                                   202
<210> 575
<211> 311
<212> DNA
<213> Homo sapiens
<400> 575
ccacagttgt atcatatagc atctctaaca tttcatctag gattatctag tatagatctt 60
actatatttg ggactatgtt gtatacaatg ttaacaagaa catatcttct ctgcatatat 120
gtgtgaatta taaagaaaag catgagaatg actctaagtt caacaaacat gggtgaatct 180
ctatgtgctc ccagtgtcct ggatgggctc cccagcaagc cattcctcct tcctgttctg 240
atattactat tcttttttac attgtgctaa ggaggacaaa agatgagaga tgaaaataaa 300
gctttqcctt t
                                                                   311
<210> 576
<211> 134
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(134)
<223> n = A, T, C or G
<400> 576
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cttcaaaagt cgct
                                                                   134
<210> 577
<211> 488
<212> DNA
<213> Homo sapiens
<400> 577
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agttgctgca aacctgaccc ctgctcagta aagcacttgc aaccgtctgt tatgctgtga 120
cacatggccc ctcccctgc caggagettt ggacctaatc caagcatccc tttgcccaga 180
aagaagatgg gggaggaggc agtaataaaa agattgaagt attttgctgg aataagttca 240
aattettetg aacteaaact gaggaattte acetgtaaac etgagtegta eagaaagetg 300
cctggtatat ccaaaagctt tttattcctc ctgctcatat tgtgattctq cctttqqqqa 360
cttttcttaa accttcagtt atgatttttt tttcatacac ttattggaac tctgcttgat 420
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ttgcattt
                                                                   488
<210> 578
<211> 476
<212> DNA
<213> Homo sapiens
<400> 578
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catcaacttg cagaaagaaa tataaatgac atttcaagga tagaagtata cctgattttt 180
ttccttttaa ttttcctggt gccaatttca agttccaagt tgctaataca gcaacaattt 240
atgaattgaa ttatcttggt tgaaaataaa aagatcactt tetcagtttt cataagtatt 300
atgtctcttc tgagctattt catctatttt tggcagtctg aatttttaaa acccatttaa 360
atttttttcc ttaccttttt atttgcatgt ggatcaacca tcgctttatt ggctgagata 420
tgaacatatt gttgaaaggt aatttgagag aaatatgaag aactgaggaa aaaaaa
<210> 579
<211> 246
<212> DNA
<213> Homo sapiens
<400> 579
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ctagaatgaa gccaccaatt tcaatgtgac caggcaatgg cagccagcac tgccttacac 120
tggtttgatt ctgattccct aattctggcc actgcaggtg atgagtaagg gtggggatca 180
gggaggaagt ccagaagcca gtctttgtct ccctttcctg cttatattta agtgcctatt 240
tacatg
<210> 580
<211> 615
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(615)
\langle 223 \rangle n = A, T, C or G
<400> 580
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atgaactgna ttcccaggag ggncacagtc cctacttttg canatgggaa agggaggtgc 120
ccaggtgtgg tcctctagac actggctccg attgctgccc ttgaggatgt agtggtcatt 180
gcacataaac gigattitgt cacttacatt cacaggccct gaagaactga actctccatt 240
caccagcaca ggatcaggac agtggcccaa gcggcactca gtagtggtgt tatcccactc 300
cttagaggca ttgcaaaaaa gggtcttctt tcctaccagg tggtagccct tgatacaaac 360
gtaagtcccc agaatctgtc cttccacctc ctttgcgaca aatatgctat tgtccactgg 420
aggaagetet ggacagtget catetgaage agaaaetege caegcaacea taagacagea 480
cgcacaccaa aaaaacatct ggtgatcaaa gtcctctccc caggctggaa ttcacccagc 540
tcagacacct tacctgtctc tgtccctcca gagttagggc ttcccancaa ggaactgggc 600
ttaactgact tccaa
<210> 581
<211> 576
<212> DNA
<213> Homo sapiens
<400> 581
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ttgtcacatc agataagaca tatctctaat tccatccata aatccagttc tactatggct 120
gagttctggt caaagaaaga aagtttagaa gctgagacac aaagggttgg gagctgatga 180
aactcacaaa tgatggtagg aagaagctct cgacaatacc cgttggcaag gagtctgcct 240
ccatgetgca gtgttcgagt ggattgtagg tgcaagatgg aaaggattgt aggtgcaagc 300
tgtccagaga aaagagtcct tgttccagcc ctattctgcc actcctgaca gggtgacctt 360
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tatattggtg gttctcagca agagaaggag tatgtgtcca atgctgcctt cccatgaatc 480
tgtctcccag ttatgaatca gtgggcagga taaactgaaa actcccattt acgtgtctga 540
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236

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576

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20 25 30 Ser Glu Glu Ala Phe Leu Thr Ile Asn Cys Thr Tyr Thr Ala Thr Gly 40 Tyr Pro Ser Leu Phe Trp Tyr Val Gln Tyr Pro Gly Glu Gly Leu Gln 55 Leu Leu Leu Lys Ala Thr Lys Ala Asp Asp Lys Gly Ser Asn Lys Gly 70 Phe Glu Ala Thr Tyr Arg Lys Glu Thr Thr Ser Phe His Leu Glu Lys 85 Gly Ser Val Gln Val Ser Asp Ser Ala Val Tyr Phe Cys Ala Pro Asn 100 105 Pro Ser Leu Gln Gly Gly Ser Glu Lys Leu Val Phe Gly Lys Gly Thr 120 Lys Leu Thr Val Asn Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr 135 140 Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr 150 155 Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val 165 170 Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys 180 185 Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala 200 Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser 215 220 Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr 230 235 Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile 245 250 Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu 265 Trp Ser Ser 275 <210> 585 <211> 312 <212> PRT <213> Homo sapiens <400> 585 Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala 10 Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu 20 25 Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu 55 Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro 70 7.5 Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg 85 90 Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser 105 Ser Tyr Ser Val Gly Glu Gly Gly Asp Ser Pro Leu His Phe Gly Asm

120

Gly Thr Arg Leu Thr Val Thr Glu Asp Leu Asn Lys Val Phe Pro Pro

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135
                                         140
Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln
     150 155 160
Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
              165 170
Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
                            185
Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
                          200
Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
                      215
Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
                 230
                                    235
Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
              245
                    250
Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser
          260
                             265
Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
                         280
Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
                     295
                                         300
Ala Met Val Lys Arg Lys Asp Phe
                  310
<210> 586
<211> 97
<212> PRT
<213> Homo sapiens
<400> 586
Glu Val Glu Val Ser Arg Asp His Ala Ser Leu Gly Asp Ser Glu Thr
                5
Leu Ser Gln Thr Glu Leu Arg Lys Lys Glu Arg Lys Lys Arg Glu
                               25
Arg Lys Phe Gln Ala Asn Cys Gly Ile Asp Phe Ile Ile Phe Trp Ile
                          40
Phe Trp Ile Leu Leu Phe Ser His His Trp Ile Gln Glu Ser Leu Leu
                      55
Cys Pro Pro Ser Pro Lys Glu Val Thr Cys Arg Glu Met Leu Thr Gly
                  70
Gly Cys Leu Pro Trp Ala Thr Arg Ser His Leu Gly Arg Arg Lys Cys
Ser
<210> 587
<211> 16
<212> PRT
<213> Homo sapiens
<400> 587
Phe Gln Ala Asn Cys Gly Ile Asp Phe Ile Ile Phe Trp Ile Phe Trp
                                 10
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